ANNALS
OF THE
RHEUMATIC DISEASES

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THE EVALUATION OF THE ROENTGENOLOGIC FINDINGS IN ARTHRITIS

By JOHN D. CAMP

THE ideal or even generally accepted classification of the arthritides does not exist. The ones in vogue are all incomplete because the cause of the majority of arthritides is in doubt. Some classifications are based on the clinician's ideas of the cause—that is, infectious, chemical and traumatic. Some names for arthritis are merely clinical designations, with little or no specific meaning (for example, rheumatoid arthritis); other classifications are based on the dominant pathologic alteration in the joints (proliferative, degenerative), and still others on the dominant roentgenographic change (atrophic, hypertrophic, destructive).

Each of these classifications has its advantage and its field of usefulness. Each has distinct limitations and none is wholly satisfactory. The classification of the internist makes little sense to the roentgenologist, unfamiliar with the criteria supposedly necessary for a diagnosis of "allergic arthritis" or "metabolic arthritis." The schema of the pathologist seems academic to the general practitioner, who can only see the outside of the joint. The designations of the roentgenologist are open to criticism because several different conditions may produce more or less identical changes in joints. An adequate classification of articular disease, therefore, hard enough at best, cannot be made with regard to the roentgenographic or any other one feature alone, but only after a careful summation of all data, clinical, chemical, and roentgenographic.

Regardless of the clinical confusion, the roentgenologist can point out certain basic alterations which occur when the joints are diseased. In the early stage of arthritis a joint may be definitely, though moderately, diseased and yet the roentgenographic findings sometimes can be negative. There may be articular pain, definite tenderness, and even slight swelling, but no osteoporosis, lessening of articular space, alteration of bony contour, or increased periarticular density may be visible. The stage or degree of the articular disease is simply too early to alter the roentgenographic appearance. The disease is

not subclinical, but it is "subroentgenographic." The only honest report that the roentgenologist can give, if he bases his diagnosis solely on the roentgenographic findings, is "negative joint." While making the roentgenogram he accidentally may have squeezed the patient's joints, and the patient's "ouch" may be considered sufficient evidence to indicate trouble; but the roentgenologist should not, in fairness to his science, borrow that bit of evidence to alter his report of what is in truth a normal-looking roentgenogram of a joint. For example, such "negative roentgenograms" are frequently encountered in cases of acute rheumatic fever, early acute gout, or serum sickness. In each case the joint may be red, tender, sometimes exquisitely so, and yet the swelling may not be sufficiently obvious in the roentgenogram to provoke comment.

The basic alterations that may be visible in roentgenograms in cases of arthritis are briefly as follows: Periarticular swelling, osteoporosis, diminution of interarticular (interosseous) space, and alterations in bony contour. The last-mentioned alteration may be either in the nature of proliferation or destruction of bone. Many of these are common to several different forms of arthritis. I shall comment on each of these basic alterations.

Periarticular swelling alone may be visible. It is revealed by an increased density of the soft tissue shadow around the joint or by an obvious increase in size of the periarticular shadow. Other alterations may be absent; when they are, the only diagnosis the roentgenologist has a right to make is "periarticular arthritis," or, better yet, "periarticular swelling." The roentgenographic evidence of synovial involvement is not always discrete, but synovial participation is suggested by increase in the density of the soft tissue nearest the intra-articular space.

The roentgenologic evidence of involvement of cartilage (destruction by invasion as in infectious, rheumatoid or atrophic arthritis or destruction by degeneration as in senescent or hypertrophic or osteoarthritis) is diminution of intra-articular (interosseous) space and irregularity of opposing surfaces.

The roentgenographic evidence of involvement of bone consists of osteoporosis, lipping of bone, marginal or subchondral proliferation of bone or destruction of bone (marginal or subchondral areas of erosion of bone).

Many different forms of arthritis may exhibit the same variety of these basic alterations as observed in roentgenograms. It is only because certain diseases of joints, which are fairly well recognised as entities, routinely present a more or less typical combination of these basic alterations that the roentgenologist can attach a name to the condition noted. A joint may be attacked by any one of a score or more of organisms. Its integrity may be violated in the course of

gout, or its continuity altered as a result of a variety of injuries of different durations and degrees. It is too much to expect that each of these insults will cast a distinctive shadow, particularly when, with each condition, there are a variety of stages and degrees. There is too much similarity in the roentgenographic and even the pathologic response of joints to these various insults to permit the roentgenograms to be interpreted too dogmatically.

The reason for this is obvious if one studies the pathologic changes in the various types of arthritis. Regardless of the insulting agent, articular tissues can only react in one of a few ways. The synovial membrane responds to insult by inflammatory exudation (in one case [mild] with cells of a chronic reaction, in another case [severe] with cells of an acute type), by fibrosis and by villous proliferation. There is no distinguishing roentgenographic characteristic of any one form of synovitis. Articular cartilage reacts to all insults by variable degrees of disappearance (from inflammatory invasion in some cases, autolytic dissolution in certain cases of sepsis, degeneration in others). Except for suggestive data supplied by the speed and extent of destruction of cartilage—that is, in cases of septic, gonorrhœal, tuberculous or rheumatoid arthritis—there is no dependable roentgenographic differentiation of the various types of cartilage destruction. The bone reacts by varying degrees of proliferation and/or destruction—marginal or subchondral, or both.

Considering these fundamental limitations in pathologic and roentgenographic response, it would seem surprising that roentgenographic distinctions in joint disease can be made as often as they can. The reason the roentgenologist has any right to dogmatise and classify is that, in spite of a general similarity of roentgenographic change, there are combinations somewhat typical of the different disease entities. This can be illustrated by the following example used by Hench.

No matter with what object one hits the note middle C, on the piano, it always reacts by that note, C (and its overtones). Inherently, that note cannot react in any other way no matter whether one strikes it with a hammer, a pencil, a stick, or a finger. However, the tone may be different, and one may guess, from the tone, to what type of blow the tone is reacting. Likewise, in the roentgenographic study of arthritis, one must not expect massive differences, markedly characteristic alterations with each of the numerous possible insults, but one may rightly study the finer shades of differentiation, the " tone " of the roentgenographic changes, in order to suggest the etiologic type. It is by a study of subtle combinations of roentgenographic changes rather than discrete gross roentgenographic changes that one may be permitted to venture a clinical and not simply a roentgenographic diagnosis. Even then error stalks on every hand.

Classifications based on Roentgenographic Data

Ignoring other classifications, the roentgenologist, using only roentgenologic evidence, would have to classify the arthritides as follows:

Periarthritis.—If there is periarticular thickening (increased density or an enlarged soft tissue shadow, or both), but no atrophy of bone, no loss of articular space, and no abnormality of bony contour, he must make a diagnosis of periarthritis. It might be an infectious periarthritis (the early stage of what later will progress to a definite intra-articular disease), or it might not be a true early arthritis, but really a periarticular fibrositis. The roentgenologist cannot distinguish between the periarthritis of rheumatic fever, of acute gout, of serum sickness, of early gonorrhœal arthritis, or early chronic or acute infectious (rheumatoid) arthritis, or of periarticular fibrositis, although the last-mentioned condition does not produce much real swelling.

Atrophic Arthritis.—If there is osteoporosis of the epiphyses and beginning of narrowing of the cartilage space, but no other abnormality of bony contour, the roentgenologist may recognise the changes as those of atrophic arthritis (clinical synonym: rheumatoid arthritis). There is probably some periarticular swelling. If there is a little marginal lipping of bone, instead of calling it atrophic and hypertrophic arthritis, he may discount the lipping and still call it atrophic arthritis. If there is considerable lipping of bone with atrophy of bone and loss of cartilage space, what should he call it? Atrophic and hypertrophic arthritis? Clinically the patient shouldn't have both, but roentgenologically he often has both. For example, an obese man with chronic infectious arthritis (atrophic or rheumatoid arthritis in the clinical sense) will often have typical atrophic changes in the hand and ankle, but in the ankle he also will have considerable proliferation of bone.

The roentgenologist cannot differentiate the atrophic arthritis seen in some cases of mild but moderately advanced gonorrhœal arthritis from the atrophic arthritis of infectious (proliferative or rheumatoid) arthritis. If one has traumatic periarthritis (stiff, painful shoulder from injury, yet no alteration in cartilage or bone, it is not "arthritis", but if the arm is immobilised long enough in a sling or at his side the roentgenogram will reveal osteoporosis in the shoulder-joint. How can this be differentiated from the early atrophic arthritis that is supposed to represent infectious (rheumatoid) arthritis?

Hypertrophic Arthritis.—When the dominant feature is marginal proliferation of bone, the roentgenologist usually discounts the osteoporosis, destruction of cartilage, and swelling of soft tissue if present, and reports a hypertrophic arthritis. A descriptive report of destruction and hypertrophic changes is more informative and correct under such circumstances.

Destructive Arthritis.—When there is not only destruction of cartilage but definite destruction of bone—that is, the destructive areas of bone and cartilage seem more dominant than the areas of overgrowth of bone—the roentgenologist usually calls it destructive arthritis, but without borrowing from the clinical data he cannot say whether it is the destructive arthritis of gonorrhœa or of severe rheumatoid arthritis or of severe osteo-arthritis as, for example, malum coxæ senilis.

Limitations to Roentgenographic Classification

There are certain objections to the use of the term " hypertrophic " arthritis as a clinical term. Hypertrophic changes (roentgenographic) are usually the dominant note of senescent arthritis (degenerative arthritis or osteo-arthritis). However, as in the case of the fat man with rheumatoid arthritis, there may be roentgenographic evidence of atrophic arthritis in the hands and some considerable atrophy of bone in the ankles, but the roentgenogram often will show considerable hypertrophic changes in the subastragaloid joint. Clinically, the case is one of rheumatoid arthritis (diffuse atrophic arthritis). If the roentgenologist sends the physician a report concerning the hand it will indicate atrophic arthritis in both the clinical and roentgenologic sense. If he sends a report concerning the foot (hypertrophic arthritis, with atrophy of bone), the physician may interpret the term hypertrophic arthritis, not in its roentgenologic sense, but in its clinical meaning, representing the syndrome variously called senescent arthritis, osteo-arthritis, and so forth. On the basis of such circumstances, papers have been written to suggest that clinical atrophic arthritis and hypertrophic arthritis often exist in the same case and may really be one disease. What was really present was clinical atrophic (rheumatoid) arthritis in all areas with roentgenologic evidence of atrophic arthritis in hands and roentgenologic evidence of atrophic plus hypertrophic arthritis in the ankle. One should not lose sight of the fact that atrophic changes are modified by weight in the weight-bearing joints and often show more hypertrophy than atrophy.

Unless one is careful to note associated atrophy of bone I do not see how the roentgenologist can consistently differentiate between the hypertrophic arthritis seen with clinical atrophic (rheumatoid) arthritis, the hypertrophic arthritis seen with gout or that seen in static arthritis (traumatic or postural arthritis). Psoriatic arthritis of the terminal phalangeal joints shows hypertrophy of bone. Primary osteo-arthritis also does, as do " baseball fingers." Typhoid arthritis of the spinal column is usually a hypertrophic arthritis, and even tuberculosis sometimes exhibits hypertrophic changes in the spinal column.

The trouble with the term " hypertrophic arthritis " is that the

roentgenologist is merely describing the chief reaction seen in the roentgenogram, whereas the clinician, getting a report of hypertrophic arthritis, may think that the roentgenologist is diagnosing the syndrome " hypertrophic " arthritis (senescent arthritis or osteo-arthritis). That is one of the reasons why gout is so often missed. The clinician has been led to expect that gout should soon produce characteristic roentgenographic changes, and when the report comes back " hypertrophic arthritis " he promptly pigeon-holes it into the syndrome of osteo-arthritis.

When the roentgenologist reports destructive arthritis, where is the clinician to put it ? " Destructive " arthritis is usually, I suppose, the late stage of severe rheumatoid (atrophic) arthritis, but it may be the end stage of gonorrhœal arthritis, severe psoriatic arthritis, tuberculous arthritis, septic arthritis, or of the severe arthritis that occurs in some cases of ulcerative colitis.

Typical Roentgenograms of Various Types of Arthritis

One should use the word " typical " instead of the terms " characteristic " and " diagnostic." When one looks from the clinical side to the roentgenographic aspect he finds certain typical changes in the various arthritides, but when he looks from the roentgenogram (first) to the patient he must be careful not to have already developed a fixed notion from the roentgenogram. I shall present a brief outline of the typical roentgenographic changes in the various forms of arthritis.

I. *Traumatic Arthritis*

A. Acute (accidental).

1. Mild trauma.
   (*a*) May be periarticular swelling only.
2. Severe trauma.
   (*a*) Some hypertrophic reaction may follow (baseball finger).
3. Very severe trauma.
   (*a*) Hypertrophic reaction and even destructive changes may follow (hip-joint).

B. Chronic (recreational, postural, static).

1. Early.
   (*a*) Usually negative findings.
   (*b*) Perhaps small swelling (tennis wrist).
2. Late.
   (*a*) Usually hypertrophic changes (prize-fighters).

II. *Chemical Arthritis*

A. Serum sickness.

1. Usually negative findings.
2. Perhaps periarticular swelling.

B. Gout.

1. Acute.
   - (*a*) Early.
     - (1) Negative bone and cartilage.
     - (2) Periarticular swelling.
   - (*b*) Late.
     - (1) Periarticular swelling.
     - (2) Perhaps hypertrophy of bone.
2. Chronic.
   - (*a*) Early.
     - (1) Periarticular swelling.
     - (2) Hypertrophy of bone.
     - (3) Some destruction of bone and cartilage.
     - (4) Small punched-out areas.
   - (*b*) Late.
     - (1) Periarticular swelling.
     - (2) Irregular, asymmetrical, dense areas (tophi) in soft tissue.
     - (3) Hypertrophy of bone.
     - (4) Destruction of bone and cartilage.
     - (5) Small and large areas of erosion.

III. *Infectious Arthritis*

A. Rheumatic fever.

1. Joints negative or periarticular swelling.
2. Never any reaction of bone or cartilage.

B. Psoriatic arthritis.

1. In general.
   - (*a*) Affects all joints.
   - (*b*) In no way diagnostically characteristic.
   - (*c*) In terminal finger-joints evidence is exactly like that of rheumatoid arthritis.
2. Early.
   - (*a*) Atrophy of bone.
   - (*b*) Periarticular swelling.

3. Later.
   (*a*) Destruction of cartilage.
   (*b*) Slight hypertrophy of bone.
4. Latest.
   (*a*) Changes of previous stages plus destruction of bone.

C. Gonorrhœal arthritis.

1. In general.
   (*a*) Evidence same as in any phase of infectious arthritis, depending on stage and severity.
2. If arthralgia only.
   (*a*) Negative findings.
3. If mild.
   (*a*) Periarticular swelling.
   (*b*) Perhaps some atrophy of bone.
4. If of moderate severity.
   (*a*) Periarticular swelling.
   (*b*) Atrophy of bone.
   (*c*) Perhaps thickening of cartilage and slight hypertrophic arthritis.
5. If severe.
   (*a*) Periarticular swelling.
   (*b*) Destruction of cartilage and ankylosis of bone (early).
   (*c*) Extent of destruction in marked relation to degree of osteoporosis and duration.

D. Arthritis of ulcerative colitis.

1. In general.
   (*a*) Not diagnostically characteristic.
   (*b*) Generally resembles mild rheumatoid arthritis (periarticular swelling, some atrophy of bone, perhaps thinning of cartilage).
2. If severe.
   (*a*) Destruction of bone and cartilage.
   (*b*) Some lipping of bone.

E. Rheumatoid (atrophic, proliferative, chronic infectious) arthritis.

1. Very early.
   (*a*) Findings may be negative.
   (*b*) Perhaps periarticular swelling.

2. Moderately early.
   (*a*) Perhaps atrophy of bone or osteoporosis.
3. Advancing.
   (*a*) Thinning of cartilage.
4. Well advanced.
   (*a*) Periarticular swelling.
   (*b*) Atrophy of bone.
   (*c*) Definite loss of cartilage.
5. Late.
   (*a*) Moderate severity.
      (1) Foregoing manifestations plus hypertrophy of bone. (N.B.—The hypertrophy affects weight-bearing joints relatively early.)
   (*b*) Severe.
      (1) Little periarticular swelling.
      (2) Severe atrophy of bone.
      (3) Cartilage destroyed.
      (4) Moderate lipping of bone.
      (5) Severe destruction of bone.
      (6) Severe disarrangement of joint.
      (7) Ankylosis.
      (8) Deformity.

F. Septic arthritis. (N.B.—Infection with staphylococci, gonococci, pneumococci, streptococci, Brucella.)
1. Early.
   (*a*) Swelling of soft tissue.
2. Advanced.
   (*a*) Swelling of soft tissue.
   (*b*) Destruction.
3. Late.
   (*a*) Destruction.
   (*b*) Hypertrophic reactions.
   (*c*) Ankylosis.

IV. *Primary Osteo-arthritis* (*Hypertrophic, Senescent, Degenerative Arthritis*)

A. In general.
1. Never ankylosis except as related to spurs.

B. Early and mild (finger).
1. Slight periarticular swelling.
2. Slight thinning of cartilage.

C. Advancing.

1. Changes of early stage plus further destruction of cartilage.
2. Beginning of definite lipping of bone.

D. Late.

1. Slight (decreased) periarticular swelling.
2. Destruction of cartilage more or less complete.
3. Marked marginal lipping of bone.
4. One or both of the following: (1) subchondral bone; (2) areas of destruction and hypertrophy.

E. Later.

1. Deformation.

Conclusions

1. In arthritis, roentgenograms alone are rarely characteristic enough to be diagnostic of any specific ætiologic condition.

2. When the roentgenologist uses the terms "atrophic," and particularly "hypertrophic," he must be sure the clinician knows he is referring to the roentgenographic image and is not diagnosing a clinical syndrome—for example, "hypertrophic arthritis" (meaning senescent or primary osteo-arthritis). The two may or may not be synonymous. This may be important in medico-legal cases.

3. The roentgenographic "diagnosis" is not final, but always subject to correlation with the clinical data.

RHEUMATIC FEVER AND NUTRITION*

By JAMES F. RINEHART

The factors controlling the development of rheumatic fever afford an intriguing medical problem and one of major importance to public health. Most investigators have concerned themselves with the bacteriological aspect of the disease. That an infective agent is operative in the development of rheumatic fever can hardly be denied. The work of numerous students strongly implicates the hæmolytic streptococcus.[1] The more recent work is particularly impressive. The common occurrence of respiratory infections with various strains of Group A hæmolytic streptococci preceding the onset of rheumatic fever

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strongly incriminates this organism as the infective agent. On the other hand evidence also indicates that some other factor or factors are operative. While respiratory infections with effective strains of hæmolytic streptococci are common, in only a small minority of cases are such infections followed by the rheumatic syndrome. A most promising line of investigation would appear to be a search for predisposing or conditioning influences. The difference in frequency of rheumatic fever at the extremes of the social economic scale has not received the thought and study which it merits. Most of such studies have come from England. Campbell and Warner[2] report that rheumatic fever is the most crippling affection of the poor. Glover[3] believes that no disease has a more clean-cut social incidence than rheumatic fever and estimates the occurrence of acute rheumatism as 20 or even 30 times as great in the poor as in the well-to-do. Miller[4] finds that, although the frequency does not seem to follow absolutely the variations in degree of poverty, " yet nothing is more certain than that it is a disease of the poorer classes." Coombs[5] notes that it is quite certainly a rare disease among the well-to-do. Among 1,000 children from the Out-Patient Department of King's College Hospital, London, the incidence of those showing evidence of acute rheumatism was 13·1 per cent., whereas among 700 children from private practice the incidence was only 0·7 per cent.,[6] a *ratio of 19 to 1.* Paul[7] finds a less striking, though distinct, association with poverty in his New Haven studies. It seems probable that less marked differences in social-economic conditions were present in the New Haven groups. There are, of course, a number of factors which might be operative in the different social environments. To the writer it appears unlikely that hereditary influences would be responsible for striking differences in "social" incidence. Although little is known with regard to the incidence of hæmolytic streptococcic infections in various social categories it also appears extremely improbable that the organism would exhibit the striking social selectivity observed in rheumatic fever. One variable factor intimately associated with social environment is undoubtedly nutritional. This has been rather clearly shown with respect to vitamin C.[8] As indicated below, very suggestive, if not conclusive, evidence has already accrued implicating nutritional deficiency as a contributory influence in rheumatic fever. If this is so, it would give the whole problem a hopeful outlook for ultimate control. Certainly this aspect of the problem deserves thorough investigation. It is the purpose of this paper to review the evidence implicating nutritional deficiency in rheumatic fever.

Vining[9] emphasised the debilitated state of the pre-rheumatic child and suggested that vitamin B undernutrition might play a rôle in the development of rheumatic fever. McLean[10] reviewed the early manifestations of the disease in 258 children. He observed that they were

commonly pale, high-strung, nervous, irritable children who were easily fatigued, had poor appetites, and who were either losing weight or not gaining it as they should.

Experimental Evidence

In 1933 we reported on a pathologic process resembling rheumatic fever, which developed in guinea-pigs subjected to the combined influence of vitamin C deficiency and infection with Beta hæmolytic streptococcus of guinea-pig origin. Heart valve and articular lesions developed which we considered to bear significant resemblance to those of rheumatic fever.[11] It is noteworthy that some of the animals even developed subcutaneous nodules analogous to those seen in the clinical disease. It is probable that this method has more closely reproduced the histopathology of rheumatic fever than any other experimental procedure.

Schultz[12] likewise produced non-purulent carditis by means of the synergistic influence of chronic scurvy and hæmolytic streptococcic infection. He said he considered that the changes only slightly resembled those seen in rheumatic fever. More recently McBroom, Sunderland, Mote and Jones,[13] as well as Taylor,[14] have recorded the occurrence of degenerative and proliferative reactions in the cardiac valves of scorbutic animals in which a factor of infection was not experimentally introduced. They observed no clear difference in those animals in which experimental infection was superimposed on the scorbutic state. It is of significance that for the most part the streptococci used by these authors were derived from human sources and were not satisfactory infecting agents for guinea-pigs. In our original work, streptococci derived from natural pathogens for guinea-pigs were used. In our own experience the virulence of the infecting organism is important in the production of the "rheumatic-like" pathologic picture. Stimson, Hedley and Rose[15] reported the finding of a proliferative endocarditis in guinea-pigs subjected to scurvy and injected with a streptococcus toxin. They state that they had previously been attracted by the possibility of a conditioning nutritional factor in rheumatic fever. In a series of puppies in which vitamin A deficiency was followed by inoculation with streptococci derived from a case of rheumatic fever, the result was negative.

Clinical Studies of Vitamin C Nutrition and Metabolism in Rheumatic Fever

In the clinical field the observations are conflicting, and to date are inconclusive. Perry[16] (1935) determined the excretion of vitamin C in the urine of rheumatic children following a single test dose of 500 mg.

of ascorbic acid. He studied 5 acute cases and 6 quiescent cases. Three in each group showed no apparent deficiency; the others were soon brought to a state of saturation by repeated test doses of ascorbic acid. While finding that " mild degrees of deficiency are not uncommon in rheumatic children," he concluded that " vitamin C deficiency is not an important factor in the causation of acute rheumatism." Sendroy and Schultz[17] reported observations on the metabolism of vitamin C in cases of rheumatic fever. Although they concluded that the results of this study did not support the concept that a condition of ascorbic acid deficiency is a predisposing factor in the causation of rheumatic fever, their results might be interpreted differently. It should be pointed out that the study was not one that evaluated the nutritional status relative to vitamin C at the *onset* of the disease. A number of the cases in the series had been given ascorbic acid supplements for one to four months prior to examination. This study, however, reveals the interesting fact that 7 of the 13 cases showed a significant metabolic abnormality, in that there was a marked discrepancy between intake and urinary excretion of ascorbic acid, indicating either a fault in absorption or enhanced destruction or utilisation of the vitamin in these cases. Abbasy, Harris and Hill[18] reported findings in a large series of cases in a study based upon urinary excretion of ascorbic acid. They found that rheumatic subjects both in the *active* and *convalescent* stages were significantly undersaturated with ascorbic acid even though they were on a diet which they had found adequate to maintain saturation in control subjects. Based upon a body weight of 140 lb. the tissue deficit of ascorbic acid in the rheumatic subjects was in the range of 2 grammes. Studies which we have recently reported lead us to believe that this may represent a significant degree of deficiency.[19] While they found a comparable condition in cases of active tuberculosis, the cases of convalescent tuberculosis reacted as the normal controls. The above findings were not borne out in a small series of cases reported by Keith and Hickmans.[20] The cause for these divergent findings is not apparent. In our experience there are many irregularities in data based solely upon urinary excretion, and a considerable urinary output may occur following a test dose of the vitamin in the presence of a low blood content and before tissue saturation has been achieved.[21]

It should be pointed out that these studies were not well adapted for determination of the degree of deficiency existing at the time of onset of the rheumatic fever. If a case of scurvy were given liberal supplements of vitamin C for several days before examination, excretion studies would naturally not reveal the pre-existing vitamin C deficiency. It is quite important, then, to take into consideration dietary modification that may have been made prior to such studies. We have attempted to do this and have based our work largely on the analysis

of the blood plasma concentration of vitamin C. It is well established that the concentration of ascorbic acid in the blood plasma clearly reflects the immediate nutritive status of the individual at the time of examination. In a series of adults[19] we have found that fasting plasma ascorbic acid concentrations below 0·1 mg. per cent. usually indicate severe tissue depletion and in approximately 80 per cent. of such cases other evidences of significant vitamin C deficiency or subclinical scurvy can be demonstrated. Blood concentration between 0·1 and 0·3 mg. per cent. reflected lesser degrees of tissue depletion, and in a smaller percentage can be shown to be suffering from subclinical scurvy. This might be considered the range of " potential " deficiency. Adult patients with plasma concentrations varying from 0·3 to 0·8 mg. per cent. show only mild tissue depletion and it appears unlikely that they are suffering from vitamin C deficiency even though the tissues are not saturated. We have previously reported observations on plasma ascorbic acid values in rheumatic fever.[21] Extended data regarding findings on rheumatic fever cases and control groups in adults are tabulated below (Table I).

TABLE I

	No. of Cases.	*Average Plasma Ascorbic Acid.*	*Distribution of Plasma Ascorbic Acid Values mg./100 c.c.*		
			0·0–0·09	0·1–0·3	*Over* 0·3
" Normal " adults ..	239	0·59	11 (5%)	29 (12%)	199 (83%)
Miscellaneous infections	176	0·37	43 (24%)	50 (29%)	83 (47%)
Acute rheumatic fever (unmodified diet) ..	19	0·16	9 (47%)	7 (36%)	3 (15%)
Acute rheumatic fever (modified diet) ..	5	0·55	—	—	5 (100%)
Acute rheumatic fever—Total	24	0·25	9 (37%)	7 (29%)	8 (33%)
Chronic rheumatic heart disease	44	0·32	12 (27%)	10 (23%)	22 (50%)

It can be seen that the average ascorbic acid concentration in the adult cases with acute rheumatic fever is strikingly low, particularly in those who had had no marked modification of diet prior to examination. In this group 37 per cent. showed the very lowest blood concentration (*i.e.*, below 0·1 mg. per cent.), which we have shown to indicate strong presumptive evidence of clinically significant deficiency,[19] and most of the remainder showed ascorbic acid values in the borderline range of deficiency.

The data in children, shown in Table II, are less striking and cannot be interpreted as readily. The average normal plasma ascorbic acid concentration in children we have found to be higher than in adults,

and we do not yet know how to accurately evaluate the plasma concentration in children. These data, *per se*, are, of course, not conclusive, though they certainly are not inconsistent with the concept that deficiency of vitamin C or associated nutritional factors may be a contributory influence in the development of rheumatic fever (Table II).

TABLE II

	No. of Cases.	*Average Plasma Ascorbic Acid.*	*Distribution of Plasma Ascorbic Acid Values mg./100 c.c.*		
			0·0-0·09	0·1-0·3	*Over* 0·3
Normal (children) ..	31	0·75	1 (3%)	2 (6%)	28 (91%)
Miscellaneous infections	144	0·49	22 (15%)	32 (22%)	90 (63%)
Tuberculosis: active ..	28	0·49	5 (19%)	5 (18%)	18 (62%)
Tuberculosis: latent ..	61	0·76	2 (3%)	5 (8%)	54 (88%)
Acute rheumatic fever (unmodified diet) ..	49	0·34	8 (17%)	19 (39%)	22 (44%)
Acute rheumatic fever (modified diet)* ..	19	0·67	—	—	19 (100%)
Acute rheumatic fever—Total	68	0·44	8 (11%)	19 (27%)	41 (60%)

Abt and his associates[22] recently reported average plasma ascorbic acid values which were slightly higher in cases of acute rheumatic fever than in scarlet fever. It must be noted, however, that the data in the two groups are not comparable, and not comparable to those reported by us. Most of the 26 children in their group with rheumatic fever and carditis had been in the hospital on a diet, which is described as excellent, for some time prior to the vitamin assay. The cases of scarlet fever were observed in another hospital, and in all instances the study was begun on, or shortly after, admission. Plasma ascorbic acid values in their cases of chronic rheumatic heart disease in a third hospital were low.

THERAPEUTIC VALUE OF VITAMIN C

Although no exhaustive study has been made of the therapeutic value of vitamin C in rheumatic fever, results recorded to date have been disappointing. Sendroy and Schultz,[17] in a carefully executed but relatively short experiment, failed to find any therapeutic benefit from administration of ascorbic acid. Several recurrences of rheumatic activity were noted in cases that had received adequate supplements of ascorbic acid for periods of 1 to 4 months. Their studies of capillary

* This group represents cases in which it was *known* that the vitamin C intake had been very considerably augmented prior to chemical assay of ascorbic acid in the blood. It is not unlikely that some in the other groups likewise had received supplements.

resistance suggested the existence of vitamin C deficiency in some but not all of the rheumatic children. Abt[22] likewise observed recurrences in cases which were receiving liberal supplements of ascorbic acid.

In a group of rheumatic children Kuttner[23] found that large doses of vitamins A, B complex, C and D *added to an ordinary well balanced diet* did not reduce the incidence of upper respiratory infection, and noted that 3 children who had received the additional vitamins for some period of time developed rheumatic manifestations following a streptococcic pharyngitis.

Faulkner[24] reported the influence upon blood formation of ascorbic acid administered in doses of 200 to 300 mg., or of orange juice in equivalent amounts, in 27 cases of rheumatic fever, 8 cases of bone tuberculosis, and 2 cases of Still's disease. Thirty of these cases showed significant reticulocyte rises following administration of the supplementary vitamin C. Although Faulkner stated that the ætiology of the infection was not the controlling factor in the reticulocyte response, it is evident that the only disease category of sufficient number to be statistically significant is the rheumatic group. It is of interest that the cases studied were receiving at least a fair supplement of vitamin C prior to the study. It is my belief that the cases showing reticulocyte rises were suffering from subclinical vitamin C deficiency. The reticulocyte responses were analogous to the reaction which follows the administration of vitamin C to patients with the anæmia of scurvy.[25] It is becoming generally recognised that administration of vitamins produces a physiological response only in the presence of deficiency.[26] No specific therapeutic effect on the course of the disease was observed by Faulkner during the one-month period of increased vitamin C administration.

The failure of vitamin C to exert a direct curative action does not imply that it is without therapeutic value. Jones[27] has observed the recent marked reduction of distressing hæmorrhagic manifestations of rheumatic fever—*i.e.*, epistaxis and purpura. He notes that "Ten years ago in a ward of 7 or 8 children with active rheumatic fever, 3 or 4 nasal packings daily were frequently necessary. This picture is now completely altered. Nose bleeds are so reasonably mild and less frequent that packing of the nose is unusual." This changed picture he is inclined to ascribe to the more liberal and intelligent use of vitamin C rich foods or ascorbic acid in the management of cases.

Parenteral Ascorbic Acid in Cardiac Decompensation of Rheumatic Fever

In 1938[22] we reported a case of recurrent rheumatic carditis with cardiac decompensation who exhibited a persistently lowered plasma ascorbic acid concentration in spite of considerable excretion of ascorbic

acid in the urine. Intravenous administration of the vitamin was followed by significant improvement in cardiac function accompanied by diuresis. A striking physiological effect was noted in a second case of fulminant rheumatic carditis in a 12-year-old girl. The plasma vitamin C concentration 5 days after admission to the hospital was zero. At this time the child was very dyspnœic and cyanotic in spite of oxygen administration. The sodium salt of ascorbic acid in dosage of 111 mg. was given intravenously every 4 hours. Within 48 hours there was marked improvement in respiration and relief of cyanosis. The plasma vitamin C concentration remained at zero 4 days after the administration of ascorbic acid was started, even though approximately 2 grammes had been given. The child succumbed one month after the onset of the recurrent attack with an acute rheumatic pancarditis. The clinical relief of dyspnœa and cyanosis in the case was, however, most striking. I believe that parenteral administration of ascorbic acid is worthy of clinical trial in desperate cases of decompensation in active carditis of this type.

The Possible Influence of Vitamin P in Rheumatic Fever

Szent-Györgi and his co-workers[28] reported the presence in extracts of Hungarian red pepper, and later in lemon juice, of a substance other than ascorbic acid which exerted a control over the number of hæmorrhages in cases of " vascular " purpura. Experimental observations in animals have been conflicting and inconclusive. However, a considerable amount of clinical data has accumulated supporting the physiological activity of this substance in increasing the capillary strength in certain types of purpura. In addition to the original work of Szent-Györgi and his co-workers, Jersild,[29] Scarborough[30] and others have contributed supporting data. It is Szent-Györgi's concept that this substance, called by him " vitamin P " (permeability factor), acted with vitamin C in maintaining the integrity of the capillary wall. He expressed the opinion that vitamin P acts in conjunction with ascorbic acid as a part of an oxidation reduction system. For several years we have been interested in the capillary strength in rheumatic diseases, and it has seemed desirable to explore the possible rôle of vitamin P. While it is clear that we have insufficient data to justify any conclusion, it seems pertinent to report briefly suggestive preliminary observations in a field that appears to be worthy of further exploration. We have administered vitamin P to 3 children suffering from acute rheumatic fever. The case records are set forth below.

Case 1.—The first case studied was that of a girl 11 years of age who entered the hospital on November 3, 1940, with a recurrent attack of rheumatic fever with manifestations of active carditis. The first episode of rheumatic fever had occurred at 7 years of age. The recurrence was of 2 months' duration on entry. The sedimentation rate on admission was accelerated (18 mm. in 17 minutes)

The plasma ascorbic acid concentration was 0·23 mg. per cent. Subcutaneous nodules were present in the scalp. The child exhibited some improvement on rest in bed. For a period of 2 months between November 21, 1940, and January 20, 1941, she was given daily intravenous injections of 500 mg. of the sodium salt of ascorbic acid. Some improvement was noted during the first month, but a mild upper respiratory infection due to a hæmolytic streptococcus precipitated a recurrence. On January 24 the rheumatic process was still active, as evidenced by an accelerated sedimentation rate (18 mm. in 30 minutes), although there had been some improvement in the cardiac function and the quality of the heart sounds. At this time the child was given vitamin P by mouth and ascorbic acid was given by mouth (150 mg. daily). From this time on there was progressive improvement. The 18 mm. sedimentation time slowed to 1 hour and 56 minutes in one month. The capillary strength as measured by the Dalldorf[31] suction method also rose.

Case 2.—This 9-year-old girl was admitted to the University of California Hospital on December 27, 1940, suffering from an acute rheumatic fever of one month's duration. On admission the plasma ascorbic acid concentration was 0·94 mg. per cent. On inquiry it was found that the child had received a daily supplement of 8 oz. of orange juice for the past 3 weeks. The sedimentation rate was rapid (18 mm. in 25 minutes), and the capillary strength was found to be low. The child was given a preparation of vitamin P by mouth. Improvement was progressive during the ensuing month. The child was discharged one month after entry with a normal sedimentation time and with no clinical evidence of active disease. The capillary strength was elevated.

Case 3.—This 15-year-old Chinese boy entered the San Francisco Hospital on May 7, 1941, with a history of onset of acute rheumatic fever 6 weeks previously. Examination revealed a pale, undernourished Chinese boy with evidence of an active rheumatic carditis. The sedimentation rate was rapid (18 mm. in 13 minutes). The blood plasma ascorbic acid value was zero. He was given a high vitamin diet and a daily supplement of 75 mg. of ascorbic acid. The rheumatic process continued to be active during the ensuing 2 months. On July 3 a tonsillectomy was done. Two weeks later the sedimentation rate remained accelerated (18 mm. in 19 minutes). On July 20 a preparation of vitamin P was administered and continued daily. The sedimentation rate progressively slowed, being 18 mm. in 40 minutes one month later. At this time he was sent to a convalescent home and the study was concluded. No effect upon the capillary strength was demonstrated.

The capillary strength has been reported as lowered in acute rheumatic fever[32] as well as in numerous other conditions. The hæmorrhagic manifestations commonly seen in rheumatic fever are well known. In view of its supposed action in conjunction with vitamin C as a part of an oxidation reduction system, and its influence on capillary strength, the possibility that vitamin P might prove useful in prevention or treatment of rheumatic fever would appear to warrant further study. Such studies are being continued by us.

Prophylactic Value of Vitamin C

The observations of Glazebrook and his associates[33, 34] are particularly interesting and afford the first direct clinical observations indicating that vitamin C deficiency may be a major disposing influence and that correction may be of great prophylactic usefulness. In 1939, Roff and Glazebrook[33] described cases of gingivo-stomatitis among

boys in a training establishment of the Royal Navy. "The gums were congested and spongy, the surfaces having a gelatinous feel. Bleeding did not occur on simple palpation, but if one pierced with a probe the hæmorrhage was more copious than usual. The congestion was uniform, from the gums into the sulci on to the buccal mucous membrane, extending backwards and involving the tonsils and pharyngeal wall as far as the eye could see." In all cases vitamin C deficiency was found, with an average ascorbic acid deficit of approximately 4 grammes. The condition responded to administration of ascorbic acid. These authors also recorded prominent symptoms of lassitude with rheumatic pains in and around the larger joints and noted that exactly similar symptoms occur in cases in which there is evidence of infection, and that such cases may later develop rheumatic fever, with true arthritis; or carditis may develop silently without further manifestations of rheumatism. They state: "It is often impossible to differentiate from the description of the symptoms of the patient a case which will clear up on saturation with vitamin C, from one which will tend to progress to rheumatism and carditis."

In a subsequent report Glazebrook and Thomson[34] recorded observations of unusual interest. The study was conducted at a training school for young men between 15 and 20 years of age. The circumstances presented a unique opportunity for study of hæmolytic streptococcic infection in a population that might be considered to be in a state of subclinical scurvy. It was estimated that the average daily intake of vitamin C per student was between 10 and 15 mg.* Recurrent waves of hæmolytic streptococcic tonsillitis afforded the factor of infection. Of the approximately 1,500 students observed in the study, 335 were given liberal daily supplements of ascorbic acid, which was added to milk and cocoa. In sample studies it is noteworthy that these youths required a total supplement of approximately 4 gm. of ascorbic acid to achieve saturation. This is the approximate tissue depletion in cases of clinical scurvy.

No significant difference in *incidence* of common colds and tonsillitis

* "The diet of the institution allowed over 4,000 calories per student per day. The food distributed was badly managed. Electric ovens were used to reheat the food, and to keep it hot whilst awaiting distribution. Often 8 hours elapsed between the time the food was cooked and its arrival on the dining tables. The minimum time that heat was applied to the food, including the original cooking and subsequent reheating, was 2 hours.

"The daily ration of potatoes was 12 oz. The vitamin C content of potatoes varies, but this quantity in the raw state should contain approximately 50 mg. A full ration of potatoes, as served on the dining tables, after cooking and reheating, was found to contain, on the average, about 4 mg.

"The other vegetables suffered an equal loss, with the exception of turnips, portions of which contained up to 6 mg. The milk was pasteurised, and ½ pint of it contained about 1·5 mg. The other cooked foods contributed negligible amounts. The total intake of vitamin C varied from about 10 to 15 mg. per student per day."

was demonstrated. The duration of illness with the common cold was not different in the two groups, averaging 6·32 days in the vitamin C treated classes and 6·4 days in the controls. However, the *duration* of illness due to tonsillitis was significantly different in the two groups. In the vitamin C treated classes the average stay in the hospital was 10·05 days and in the control groups 16·7 days.

The most striking influence of vitamin C was in the reduction of the incidence of two complications of the streptococcic infection. There were 17 cases of " pneumonia " and 16 cases of acute rheumatism among the 1,100 controls and no case of either disease among 335 youths having vitamin C. Analyses showed that a difference as great or greater than this would be expected once in fifty times in a homogeneous population. The authors felt that there was some relationship between the cases of pneumonia and those of rheumatic fever. They noted the occurrence in the institution of a low-grade basal lung consolidation or pneumonitis which appeared to be related to both rheumatism and vitamin C deficiency. " It was characterised on the one hand by its tendency to progress into rheumatism, and on the other hand by its disappearance when treated with ascorbic acid. This pneumonitis, apart from a vague picture of ill-health, gave little clinical evidence of its presence, but it probably predisposed toward the development of acute pneumonia."

Hedley[35] has recorded an apparent diminution of the incidence of rheumatic heart disease among persons 5 to 24 years of age during the period 1930 to 1936 compared with 1922 to 1929. It is possible that increased knowledge of the importance of nutrition to health and the emphasis upon the possible rôle of nutritional deficiency in rheumatic fever may be responsible for this decline.

Summary

Evidence is strong that respiratory infections with effective strains of Beta hæmolytic streptococci commonly precede the development of acute rheumatic fever. However, it is almost clear that some other factor enters into the ætiology of the disease. It is only a relatively small proportion of such infections that are followed by rheumatic fever. This suggests an environmental influence. The social incidence definitely associates the disease with poverty. It is doubtful that streptococcic infection would show such striking social selectivity. One of the basic environmental factors associated with poverty is, of course, nutritional inadequacy. That vitamin C undernutrition is frequently seen in the poorer classes is well attested by recent surveys. The accumulated evidence cited makes an undeniably strong case for a contributory scorbutic influence in rheumatic fever. The concept has the solid foundation of experimental evidence. Vitamin C de-

ficiency combined with streptococcic infection in the guinea-pig produces a pathological picture with many similarities to that of rheumatic fever. Both scurvy and rheumatic fever basically involve degenerative changes in connective tissues.

Studies of nutritional status relative to vitamin C in rheumatic fever, while not conclusive, certainly are not inconsistent with the concepts. While it has been shown that vitamin C does not exert a specific curative effect upon rheumatic fever it is likely that the frequency and severity of the hæmorrhagic manifestations have been reduced. It is not known to what extent vitamin C or related factors might further protect the patient. Maintenance of *rheumatic* patients on adequate amounts of ascorbic acid will evidently not prevent recurrence of the disease. However, data are cited which strongly suggest that adequate intake of vitamin C exerts a protective effect in an unselected group even though they are subjected to the influence of hæmolytic streptococcic infection.

Preliminary report is made of encouraging observations relative to the possible influence of vitamin P upon the course of the illness. It is evident that there is much data indicating that nutritional deficiency factors may be of major importance in favouring the onset of rheumatic fever. In view of the great importance of this disease studies in the field of nutrition should be extended.

REFERENCES

1. (*a*) GLOVER, J. A.: "Incidence of Acute Rheumatism," *Lancet*, 1930, **1**, 499.
   (*b*) SCHLESINGER, B.: "The Relationship of Throat Infection to Acute Rheumatism in Children," *Arch. Dis. Child.*, 1930, **5**, 411.
   (*c*) GLOVER, J. A., and GRIFFITH, F.: "Acute Tonsillitis and Some of its Sequels: Epidemiological and Bacteriological Observations," *Brit. Med. Journ.*, 1931, **2**, 521.
   (*d*) COLLIS, W. R. F.: "Acute Rheumatism and Hæmolytic Streptococci," *Lancet*, 1931, **1**, 1341.
   (*e*) SHELDON, W.: "On Acute Rheumatism following Tonsillitis," *Lancet*, **1**, 1337.
   (*f*) BRADLEY, W. H.: "Epidemic Acute Rheumatism in a Public School," *Quart. Journ. Med.*, 1932, **1**, 79.
   (*g*) COBURN, A. F., and PAULI, R. H.: "Studies on the Relationship of *Streptococcus hæmolyticus* to the Rheumatic Process. III. Observations on the Immunological Responses of Rheumatic Subjects to Hæmolytic Streptococcus," *Journ. Exper. Med.*, 1932, **56**, 651.
   (*h*) COBURN, A. F., and PAULI, R. H.: "Studies on the Immune Response of the Rheumatic Subject and its Relationship to Activity of the Rheumatic Process. II. Observations on an Epidemic of Influenza followed by Hæmolytic Streptococcus Infections in a Rheumatic Colony," *Journ. Exper. Med.*, 1935, **62**, 137.
   (*i*) COBURN, A. F., and PAULI, R. H.: "III. Observations of the Reaction of a Rheumatic Group to an Epidemic Infection with Hæmolytic Streptococci of a Single Type," *Ibid.*, 1935, **62**, 159.

(*j*) KUTTNER, ANN G., and KUMWIEDE, ELMA: "Observations on the Effect of Streptococcal Upper Respiratory Infections in Rheumatic Children: A Three-Year Study," *Journ. of Clin. Invest.*, 1941, **20**, 273.

(*k*) GREEN, C. A.: "Hæmolytic Streptococcal Infections and Acute Rheumatism," *Ann. Rheum. Dis.*, **3**, 4.

2. CAMPBELL, M., and WARNER, E. C.: "A Study of Rheumatic Disease in Children," *Lancet*, 1930, **1**, 61.

3. GLOVER, A.: "Discussion on the Etiology of Acute Rheumatism and Chorea in Relation to Social and Environmental Factors," *Proc. Roy. Soc. Med.*, 1934, **27**, 953.

4. MILLER, R.: "Reports on the Environmental and Other Predisposing Causes of Rheumatic Infection," Suppl., *Brit. Med. Journ.*, 1926, **2**, 72.

5. COOMBS, C. F.: "Rheumatic Infection of Childhood," *Lancet*, 1927, **1**, 579, 634.

6. "Child Life Investigations: Social Conditions and Acute Rheumatism." Special Report Series of the Medical Research Council, No. 114, 1927. London: His Majesty's Stationery Office.

7. PAUL, JOHN R.: "Rheumatic Fever in New Haven," 1941, Science Press, Lancaster, Pennsylvania.

8. (*a*) HARRIS, LESLIE: "Assessment of the Level of Nutrition: Tests for Vitamin C on Groups of Poorly Fed and Well-Fed School Children" (from the Nutritional Laboratory, University of Cambridge, and Medical Research Council), *Lancet*, 1940, **2**, 259.

(*b*) AHLBORG, NILS-GUNNAR, and BRANTE, GUNNAR: "Parallel Investigations into the Ascorbic Acid (Vitamin C) Content in the Blood Plasma and into the Strength of the Cutaneous Capillaries in Healthy Children," *Acta Medica Scandinavica*, 1940, civ., fasc. VI., 540.

(*c*) KAHN, NAJIB U., and MINN, M.: "Capillary Fragility and Vitamin C in 40 Children of Different Classes," *Brit. Med. Journ.*, 1941, **1**, 752.

(*d*) CRANE, MARIAN M., and WOODS, P. W.: "A Study of Vitamin C Nutrition in a Group of School Children," *New Eng. Journ. Med.*, 1941, **224**, 503.

9. VINING, C. W.: "The Pre-rheumatic Child," *Med. Jour. and Rec.*, 1928, **128**, 351, 395, and 453.

10. MCLEAN, C. C.: "Early Manifestations of Rheumatic Infections in Young Children," *Ann. Int. Med.*, 1932, **5**, 1357.

11. (*a*) RINEHART, J. F., and METTIER, S. R.: "The Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection," *Amer. Journ. Path.*, 1934, **10**, 61.

(*b*) RINEHART, J. F., CONNOR, C. L., and METTIER, S. R.: "Further Observations on Pathologic Similarities between Experimental Scurvy Combined with Infection and Rheumatic Fever," *Journ. Exp. Med.*, 1934, **59**, 97.

12. SCHULTZ, M. P.: "Cardiovascular and Arthritic Lesions in Guinea-Pigs with Chronic Scurvy and Streptococcic Infections," *Arch. Path.*, 1936, **21**, 472.

13. MCBROOM, JOSEPHINE, SUNDERLAND, DOUGLAS A., MOTE, JOHN R., and JONES, T. DUCKETT: "Effect of Acute Scurvy on the Guinea-Pig Heart," *Arch. Path.*, 1937, **23**, 20.

14. TAYLOR, S.: "Scurvy and Carditis," *Lancet*, 1937, **1**, 973.

15. STIMSON, A. M., HEDLEY, O. F., and ROSE, E.: "Notes on Experimental Rheumatic Fever," *U.S. Pub. Health Rep.*, 1934, **49**, 361.

16. PERRY, C. B.: "Rheumatic Heart Disease and Vitamin C," *Lancet*, 1935, **2**, 426.

17. SENDROY, J., JR., and SCHULTZ, M. P.: "Studies of Ascorbic Acid and Rheumatic Fever," *Journ. Clin. Invest.*, 1936, **15**, 369.

18. ABBASY, M. A., HILL, N. GRAY, and HARRIS, LESLIE J.: "Vitamin C and Juvenile Rheumatism," *Lancet*, 1936, **2**, 1413.

19. RINEHART, J. F., and GREENBERG, L. D.: "The Detection of Subclinical Scurvy or Vitamin C Deficiency," *Ann. Int. Med.*, 1942, **17**, 672.

20. KEITH, J. D., and HICKMAN, EVELYN M.: "Vitamin C Excretion in Children, with Particular Reference to Rheumatic Fever," *Arch. Dis. Child.*, 1938, **13**, 125.

21. RINEHART, J. F., GREENBERG, L. D., OLNEY, MARY, and CHOY, F.: "Metabolism of Vitamin C in Rheumatic Fever," *Arch. Int. Med.*, 1938, **61**, 552.

22. ABT, ARTHUR F., HARDY, L. MARTIN, FARMER, CHESTER J., and MAASKE, JESSIE D.: "Relation of Vitamin C to Scarlet Fever, Rheumatic Infections and Diphtheria in Children," *Amer. Journ. Dis. Child.*, 1942, **64**, 426.

23. KUTTNER, ANN G.: "The Effect of Large Doses of Vitamin A, B^1, C, and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children," *Journ. Clin. Invest.*, 1940, **19**, 809.

24. FAULKNER, JAMES M.: "The Effect of Administration of Vitamin C on Reticulocytes in Certain Infectious Diseases," *New Eng. Journ. Med.*, 1935, **213**, 19.

25. METTIER, S. R., MINOT, G. R., and TOWNSEND, W. C.: "Scurvy in Adults, especially the Effect of Food Rich in Vitamin C on Blood Formation," *Journ. Amer. Med. Assoc.*, 1930, **95**, 1089.

26. MOLITOR, HANS: "Vitamins as Pharmacological Agents," *Feder. Proc.*, 1942, **1**, 309.

27. JONES, T. D.: "Clinical Features of Rheumatic Fever and Rheumatic Heart Disease," Read at Post-Graduate Symposium on Heart Disease, San Francisco Heart Committee, November 5, 1942.

28. ARMENTANO, L., BENTSÁTH, A., BÈRES, T., RUSZNYÁK, STEFAN, and SZENT-GYÖRGYI, ALBERT: "Uber den Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren. Vitamin P," *Deutsche Med. Wchnschr.*, 1936, **62**, 1325.

29. JERSILD, TORBEN: "Therapeutic Effect of Vitamin P in Schönlein-Henoch Purpura," *Lancet*, 1938, **1**, 1445.

30. SCARBOROUGH, HAROLD: "Deficiency of Vitamin C and P in Man," *Lancet*, 1940, **2**, 644.

31. DALLDORF, G.: "A Sensitive Test for Subclinical Scurvy in Man," *Amer. Journ. Dis. Child.*, 1933, **46**, 794.

32. BROWN, EDWARD E., and WASSON, VALENTINA P.: "Capillary Resistance in Rheumatic Children," *Journ. of Ped.*, 1941, **18**, 328.

33. ROFF, F. S., and GLAZEBROOK, A. J.: "The Therapeutic Application of Vitamin C in Peridental Disease," *Journ. Roy. Nav. Med. Serv.*, 1939, **25**, 340.

34. GLAZEBROOK, A. J., and THOMSON, SCOTT: "The Administration of Vitamin C in a Large Institution and its Effect on General Health and Resistance to Infection," *Journ. of Hygiene*, 1942, **42**, 1.

35. HEDLEY, O. F.: "Trends, Geographical and Racial Distribution of Mortality from Heart Disease among Persons 5-24 Years of Age in the United States during Recent Years," *U.S. Pub. Health Rep.*, 1939, **54**, 2271.

VISCERAL LESIONS ASSOCIATED WITH RHEUMATOID ARTHRITIS

By DAVID L. FINGERMAN and FRANK C. ANDRUS

I. Criteria Used in Selection of Cases

In the study of the visceral lesions in rheumatoid arthritis, the records of 192 cases having a diagnosis of arthritis were examined. These cases were obtained from the autopsy files of the University of Minnesota Pathology Department and associated local hospitals. Out of this group there were 81 which were frank suppurative arthritis, 61 were rheumatoid arthritis, and 29 were osteo-arthritis. There were 8 with tuberculous arthritis; 7 had a simple, chronic, non-suppurative, non-specific arthritis of undetermined ætiology and involving only one joint; five had an acute inflammatory, non-suppurative arthritis, type undetermined, and 1 had gonorrheal arthritis.

" Rheumatoid Arthritis " as discussed in this paper is the severe deforming type of chronic infectious arthritis. It is the atrophic, proliferative type of arthritis. The criteria used in selecting these cases of rheumatoid arthritis were as follows: The disease must have been chronic, being present a minimum of several months. It must involve two or more joints. It must have caused deformities of the joints and their adjacent structures, and finally, it must be of a non-suppurative type of involvement. That is, all cases which showed frank pus or definite ætiological factors or trophic changes such as syphilis, trauma, syringomyelia, tuberculosis, gonorrhea, suppurative streptococcus and staphylococcus infections involving joints were immediately excluded. However, the differentiation and exclusion of osteo-arthritis or hypertrophic (degenerative) type of arthritis from the rheumatoid or atrophic (proliferative) type of arthritis was not so simple. Any cases which had mixed types of arthritis or different types of arthritis in different joints were not included. That is, if a case was found to have both proliferative and degenerative changes, it was omitted from the series. The distinction was made by the clinical, radiological, and pathological evidence available. On this basis, 61 cases of rheumatoid arthritis were obtained and were studied with regard to their visceral lesions.

II. Terminology

Chronic arthritis was classified in 1905 by Richardson into two main types: (1) Proliferative and (2) degenerative. However, since then other terms have been introduced which have been used interchangeably with the above two. Proliferative arthritis is often named

atrophic or rheumatoid arthritis, and degenerative arthritis is often spoken of as hypertrophic or osteo-arthritis. The reason for the variability in terminology is that the clinician uses one classification, the pathologist another, and the roentgenologist yet another, and so on. For example, the terms "atrophic" and "hypertrophic" arthritis are primarily for the roentgenologist, who designates as atrophic that type which refers to bony atrophy, erosion, and destruction, and hypertrophic to eburnation and bone production with spur formation.

It might be added that it would be impossible to classify arthritis on an ætiological basis, since not all the ætiological factors are known and different ætiological agents appear to be able to give similar pathologic pictures—*e.g.*, gonorrheal arthritis may simulate "non-specific" proliferative arthritis (Allison and Ghormley).

III. Joint Pathology

In proliferative arthritis, as described by Richardson, Nichols, and others, there is proliferation of the synovial membrane and the perichondrium with the formation of a layer of granulation tissue over the joint surface as a thin, pannus-like layer. The pannus may cause a destruction of the articular cartilage, and as a result the joint space may disappear with the development of a fibrous or a bony ankylosis. At the same time, there may also be a proliferation of the connective tissue in the epiphyseal marrow spaces and proliferation of the endosteum of the epiphysis. This process can also invade the articular cartilage from below, and thereby help destroy it.

In degenerative arthritis, the primary changes are a degeneration and fibrillation or splitting of the hyaline cartilage of the articular surfaces with erosion and exposure of the underlying bone, thus forming an irregular articular surface. Often there is a corresponding overgrowth of cartilage or bone on the opposite surface with spur formation. Due to the irregular surfaces, a pseudo-ankylosis from locking of the joint may occur, but never true ankylosis.

The anatomic changes in rheumatoid arthritis may be described briefly as follows: The disease may start out as an acute process with rapid destruction of the joints, or it may be very slowly progressive. The microscopic picture can vary from one showing neutrophilic infiltration to one showing round cell infiltration; or even fibrous scarred areas may be present.

The rheumatoid arthritis which we will discuss is the severe deforming advanced form of proliferative arthritis in which there are contractures, ankyloses, and atrophy of the extremities present.

IV. Incidence

There are no figures available as to the exact incidence of rheumatoid arthritis. However, it is a common disease in the general population. The Ministry of Public Health in London states that in any 1,000 insured males of all ages there will be 1 case of proliferative arthritis, and that in any 1,000 insured females there will be 3 cases. This sex ratio of 3 to 1 is confirmed by other authors (Allison and Ghormley), but many do not find such a high proportion of females. In 110 cases studied by McCrae at Johns Hopkins Hospital, there was an equal distribution of females and males. In our series, we had a slight predominance of females, numbering 34 females and 27 males. However, the ratio of autopsies done on males to females at the University of Minnesota Pathology Department is approximately 2 males to 1 female. Thus, the normal distribution, females to males, as obtained from our series, would be 68 females to 27 males.

There is a wide variation in the age ranges. Our youngest patient was 10 years and the oldest 87 years of age. However, over three-fourths of the cases were between 40 and 80 years of age. The duration of the disease varied from 6 months to 35 years with the average duration being between 5 to 10 years. This age incidence is somewhat higher than that reported by other authors. Allison and Ghormley state that the average age of onset is 20 to 40 years. Others claim that it does become manifest before 35 years.

Our age group, from autopsy material, represents the time of death, which will be a later age than that reported by clinicians.

With regard to race, nothing remarkable was noted. There were 3 negroes in this series.

The effect of climate on chronic arthritis has not yet been determined (Hench *et al.*). In Europe, it is as common in northern Sweden as in Holland or Denmark. One does not see the striking geographical contrast in this disease that one sees in rheumatic fever, which is much more frequent in the north.

V. Joints Involved

On analysis of the joints affected in rheumatoid arthritis, it was found that the knees were involved most commonly, 42 cases, being followed in frequency by the hands, 34 cases, feet 20, ankle 15, elbows 15, hips 12, wrists 10, shoulders 9, and spine 4 Allison and Ghormley list sites of involvement in the following order: first feet and hands, then wrists, ankles, elbows, knees, hips, shoulders, jaw, and spine. The distribution is usually symmetrical, however. This is in contrast to osteo-arthritis, which is rarely symmetrical.

VI. Cause of Death

The causes of death in this series were varied. The most common cause was bronchopneumonia, which occurred in 24 cases. The next most common cause was septicemia and pyemia, which occurred in 9. The other common causes of death in order of their occurrence were lobar pneumonia (8 cases), tuberculosis (7), carcinoma (3), amyloid disease (3), cardiac decompensation (3), and uremia (2).

VII. Cardiac Lesions

The cases having rheumatic heart disease were separated and analysed. Out of the total of 61 cases, 19 had rheumatic heart lesions. In other words, 31 per cent. of the patients were found to have fibrous adhesive pericarditis, aortic, mitral, or tricuspid valvular involvement and combinations thereof of a rheumatic nature. Most of these lesions were old healed valve defects of varying degrees of deformity with thickening and retraction of the leaflets, thickening and shortening of the chordæ tendinæ, and fusion of the commissures. The mitral valve was most commonly affected, with 16 out of 19 persons having rheumatic mitral valve lesions. One mitral valve had an acute rheumatic involvement, while the remainder had old deformed rheumatic defects. The aortic valve had lesions in 11, 2 of which were of the calcified nodular type. There was a fibrous adhesive pericarditis in 7. The myocardium in 2 patients showed an acute diffuse myocarditis, with many mononuclear cells present; 1 had several Aschoff nodules; 1 had tricuspid valvulitis together with a rheumatic mitral valve disease. There were 2 instances of superimposed terminal acute bacterial endocarditis, with one involving both the aortic and mitral valve, and the other affecting only the mitral valve (Chart I., p. 29).

Only 6 of the 19 patients showed signs of myocardial insufficiency with chronic passive congestion of the liver, ascites, and œdema; and cardiac decompensation was thought to be a primary cause of death in 3 cases.

In February, 1941, Baggenstoss and Rosenberg studied 25 cases of chronic infectious (*i.e.*, rheumatoid) arthritis. All of their patients had progressive polyarticular inflammation. In these cases, 20 had associated cardiac damage. Lesions that were regarded as being identical with those produced by rheumatic fever were found in 14 of the 20; 5 of the 20 cases had non-rheumatic lesions. These 5 lesions were as follows: (1) Coronary sclerosis with thrombosis and acute and chronic infarction of the myocardium. (2) Non-specific subacute fibrinous pericarditis. (3) Cardiac hypertrophy with hypertension. (4) Coronary sclerosis with chronic infarction of the myocardium. (5) Hydropericardium. The remaining one had a fibrous obliterative pericarditis,

but the nature of this lesion could not be determined because neither the heart nor the histologic sections were saved. In this series, cardiac disease was considered a primary or important cause of death in 7 of the 14 cases in which rheumatic lesions were found at autopsy.

Baggenstoss and Rosenberg believe that the high incidence of rheumatic cardiac lesions suggested a relationship between chronic infectious arthritis and rheumatic fever. They felt that the cardiac lesions associated with chronic infectious arthritis are not quite as severe or widespread as those lesions in hearts of young persons who have rheumatic fever; however, the differences are of degree and not of kind. Only 2 of the University of Minnesota series having cardiac lesions had had episodes of rheumatic fever prior to developing deforming arthritis. Of the cases with valve deformities, only 7 of these cases were described as having characteristic murmurs.

Examination of the blood pressure readings in the total series of rheumatoid arthritis revealed that few of the patients had hypertension. In fact, there seemed to be a tendency for them to have hypotension. Only 1 case had a diastolic pressure over 100 mm. of mercury with a systolic over 180 mm. of mercury. There were only 6 cases in which the diastolic pressure was between 90 and 100 and the systolic between 150 and 180. The majority of the cases were between 150/90 to 110/70, while there were 9 cases with pressures less than 110/70. The cases with cardiac lesions seemed to follow the same proportionate grouping.

It must be remembered that most of these patients were bedridden for some time before death and some of them were moribund; this may explain the tendency toward hypotension.

Cardiac lesions have long been known to be associated with rheumatoid arthritis. Todd in 1853 was probably the first to mention the relationship. Boas and Rifkin studied 80 cases of rheumatoid arthritis at the Montifiore Hospital and found clinical signs of valvular heart disease in 14 out of their 80 cases, or 17·5 per cent. Their criteria were a diastolic murmur (aortic or mitral) or a systolic apical murmur with cardiac enlargement, excluding hypertension and other causes.

Still, who described in 1896 the chronic joint disease in children known as Still's disease, noted cardiac lesions. This disease he defined as a chronic progressive enlargement of the joints associated with generalized lymphadenopathy and splenomegaly. Actually it seems to be a juvenile type of rheumatoid arthritis. He noted an adherent pericardium in 3 out of 12 cases which came to autopsy, and that 1 had a thickened mitral valve.

In 1924, T. W. Froggatt studied 50 patients having chronic infectious arthritis to determine how many had physical signs of heart disease. On the basis of heart murmurs, dilatation of the heart, and symptoms, he found 14 of them to have cardiac abnormalities.

Since that time several authors have noted a relationship between

CHART I.—CARDIAC LESIONS

Case No.	*Fibrous Adhesive Pericarditis.*	*Aortic Valve Lesion.*	*Mitral Valve Lesion.*	*Tricuspid Valve Lesion.*	*Myocardial Lesion.*
1	Present	Old valve defect, superimposed bacterial endocarditis	Old valve defect, superimposed bacterial endocarditis		
2			Old valve defect	Old valve defect	
3	Present		Acute bacterial endocarditis		
4		Old valve defect	Old valve defect		
5	Present	Ditto	Ditto		
6	Present	Ditto	Acute rheumatic endocarditis		
7			Old valve defect; mitral stenosis		
8			Old valve defect		
9	Present	Ditto	Ditto		
10		Ditto			
11			Old valve defect; mitral stenosis		
12		Old valve defect; stenosis and insufficiency	Old valve defect; stenosis and insufficiency		
13		Old valve defect	Old valve defect		
14			Ditto		
15			Ditto		
16		Calcified nodular	Ditto		
17		Old valve defect; stenosis and insufficiency			Acute diffuse myocarditis with Aschoff nodules
18	Present		Ditto		
19	Present	Calcified nodular	Ditto		Acute diffuse myocarditis

chronic infectious or rheumatoid arthritis and acute rheumatic fever. M. H. Dawson made a comparative study of the subcutaneous nodules in rheumatic fever and rheumatoid arthritis and found the nodules presented striking similarities; and he advanced the hypothesis that the lesions are manifestations of the same fundamental pathological processes. In frequency the subcutaneous nodules occur in acute rheumatic fever in 10 to 50 per cent. of cases, while in infectious arthritis, Clawson and Wetherby have found that the nodules were present in over 25 per cent. of 800 cases. Both types of lesions have focal necrosis and inflammatory cell infiltration in the early stages. Later the collagen fibres in the centre of the nodules swell and form a central hyaline fibrinoid material. Dawson stated that the size of these nodules is proportionate roughly to the length of the disease. Usually, in acute rheumatic fever, the nodules are about 5 mm. in diameter, while in rheumatoid arthritis they vary between 1 to 2 cm. in diameter. The appearance of these nodules is generally associated with a severe form of their respective diseases, especially in acute rheumatic fever, in which the presence of nodules is indicative of cardiac damage (Dawson).

VIII. Laboratory Data

An analysis of the laboratory data in this group of 61 arthritics revealed that some of them had anæmia. The hæmoglobin varied between 50 and 100 per cent., with the average between 70 and 80 per cent. The erythrocyte count was reduced accordingly.

Chart II.—Hæmoglobin

Hæmoglobin Percentage.	*Cases.*
100-90%	5
90-80%	8
80-70%	15
70-60%	7
60-50%	7
50-40%	3

The urine from 28 of the patients contained albumin, leucocytes, and erythrocytes; however, 13 of these had only a faint trace of albumin.

Chart III.—Urinalyses

		Cases.
1	Albumin—faint trace	13
2	Albumin—1+	6
3	Albumin—2+	6
4	Albumin—3 to 4+	3

The kidneys at autopsy showed no marked abnormalities grossly. The combined weights ranged from 150 to 350 grammes, with the largest

group (17) having their total weight between 200 and 250 grammes. Grossly only 19 cases had a uniform type of abnormality, that is, granular pitted surfaces with adherent capsules. Microscopically the kidneys from 8 patients showed glomerulitis with moderate to marked increase in endothelial nuclei; 2 of these had had clinical signs of glomerulonephritis. Most of the patients in this group had some sort of concomitant infection such as decubital ulcers (18 cases), pneumonia (31 cases), and septicemia (9 cases).

The leucocyte count showed a wide range of variation. There were 3 with counts of less than 4,000, one of them being 1,400; 6 cases were below 5,000. There were 22 cases whose counts were between 4,000 and 10,000, and there were 20 cases which were above 10,000, with 6 of these between 20,000 and 30,000. (See Chart IV below.)

CHART IV.—LEUCOCYTE COUNTS

	Cases.
1,000- 4,000	3
4,000- 5,000	3
5,000- 6,000	2
6,000- 7,000	9
7,000- 8,000	3
8,000- 9,000	1
9,000-10,000	4
10,000-15,000	11
15,000-20,000	2
20,000-30,000	6
Over 30,000	1

The patients who had high leucocyte counts invariably had some other infectious process present such as a septicemia or pneumonia. Of the patients who had leucopenia, 2 had Felty's syndrome.

IX. SPLENIC LESIONS

In 1924, Felty described 5 cases which were strikingly similar in that they all had chronic arthritis, splenomegaly, and leucopenia. In 3 of the 5 there was brownish pigmentation of the skin and generalised lymphadenopathy. These features are usually included in the syndrome.

Felty's syndrome as a disease entity has been subject to some question in recent years. In 1940, Curtis and Pollard compared the tissue changes in Felty's syndrome with other forms of rheumatoid arthritis. They believed rheumatoid arthritis to be a generalised disease which affects other tissues such as the skin, muscle, spleen, liver, lymph-nodes, and bone marrow, as well as the joints. They stated that Felty's syndrome is merely one particular symptom complex of the disease and not a clinical entity, and that it occurred merely as a matter of chance. These men had 11 arthritics which were divided into three groups. Group I consisted of 4 cases that had all

the cardinal symptoms as described by Felty. Group II was a controlled group that had arthritis and splenomegaly; however, it had a leucocytosis instead of a leucopenia. Group III had rheumatoid arthritis but no palpable spleen or leucopenia.

Biopsies of the skin and muscles of the calf were made and compared in these patients. All of the groups were the same, and one could not be distinguished from the other microscopically. In general the biopsies showed atrophy of the epithelium, fibrosis of the corium, increase in interstitial nuclei of the muscle fibres, and small perivascular infiltration through the corium and muscle. These men felt that splenomegaly and leucopenia were two of the multiple findings that may occur with chronic infectious arthritis. They saw no justification for the separation of those cases having arthritis, splenomegaly, and leucopenia into a specific syndrome. Since it was merely a matter of chance, they thought that the use of the term " Felty's syndrome " should be discontinued.

In our series of 61 patients, 3 had Felty's syndrome. However, there were 6 other cases which had splenomegaly along with the arthritis deformans but who did not have leucopenia. The weight of the spleens in most of our cases varied from 75 to 300 grammes, the majority of them (32) being between 100 and 200 grammes. Nine weighed over 300 grammes and 4 of them over 500 grammes.

Chart V.—Weights of Spleens

Grammes.	*Cases.*
0-100	8
100-150	16
150-200	16
200-250	2
250-300	5
300-350	3
350-400	2
Over 400 (520, 775, 700, 1,475)	4

As far as actual pathology in the spleen itself was concerned, there was nothing remarkable to note: 8 cases showed hyaline perisplenitis; a few were congested; 11 of the spleens had amyloid in them in association with amyloid deposits in other organs of the body, and 2 of these were over 300 grammes. Amyloidosis will be discussed later.

X. Bacteriologic Findings

Bacteriologic findings also seem to point to some relationship between rheumatoid arthritis and rheumatic fever. Dr. Clawson has cultured the subcutaneous nodules seen in rheumatoid arthritis and has shown that the macerated nodules yielded organisms which were the same as those from the blood of patients having rheumatic fever. He

also noted that structurally the nodules seemed to be similar to those found in acute rheumatic fever and to those produced in animals by injecting streptococci.

In 1936 Singer and Levy reported 2 cases of Felty's syndrome in which they isolated *Streptococcus viridans* from blood culture. They felt that Felty's syndrome was due to chronic, low-grade sepsis, probably streptococcic. Their 2 cases were described in detail, especially the microscopic examination. They thought that the anatomic changes represented the effects of a long-standing low-grade infection, and they felt that they were typical of the alterations observed in sepsis lenta. These changes included activation of the endothelium, noted especially in the spleen and lymph-nodes and indicated by swelling, increase in number, and desquamation of the endothelial cells. They also noted erythrophagocytosis, increased plasma cells in the spleen and lymph-nodes, and particularly in the bone marrow. They also observed a decrease in the bone marrow elements, notably the granulocytes.

Microscopic examination from the skin of the thigh showed a great deal of iron pigment in the cutis. There were iron-containing cells particularly evident about the sweat glands which were in the form of heavy coats. The adventitial cells of the cutaneous capillaries were engorged also with iron granules. The melanin in the basal layers of the epidermis was not increased, however. This change probably accounts for the pigmentation.

Also noted were the microscopic findings of subacute glomerulonephritis and evidence of myocarditis. The glomeruli of the kidneys were cellular and the basal membranes were slightly thickened. Occasional fibrous crescents were seen and some of the glomeruli were partially hyalinized. Many of the tubules were filled with blood or hyaline casts, and the tubular epithelium was swollen and granular in places. The myocardium had increased amounts of connective tissue around the larger vessels, and it was loose and œdematous. It contained many swollen fibrocytes and loosely scattered lymphocytes and plasma cells. The muscle fibres were free of fat and the cross striations were indistinct. One of the cases showed typical Aschoff bodies in the myocardium. The authors state, as Dr. Clawson pointed out, that although the Aschoff nodule is characteristically noted in rheumatic fever, it is not limited to that disease.

From the evidence obtained in these cases, Singer and Levy state that Felty's and related syndromes are special forms of sepsis lenta. They believe that the underlying sepsis affects not only the joints but also the hæmatopoietic system—that is, the spleen, liver, bone marrow, and the lymph-nodes. The variable response of the different tissues of the host determines the symptomatology and accounts for the different clinical pictures observed. The ætiologic agent is believed

to be a streptococcus of the viridans type. It is likely that other bacteria can occasionally produce Felty's and allied syndromes.

Some of our evidence could be readily applied in support of the hypothesis advanced by these authors, since we have found a variable picture in all of our cases of rheumatoid arthritis. That is, some had leucopenia and others did not; some had splenomegaly and others did not, etc. This evidence also seems to support the idea of Curtis and Pollard that Felty's syndrome is not a disease entity.

XI. Pleuræ, Lungs, and Liver

Examination of the pleuræ, lungs, and liver gave the following findings in our series. There was a marked fibrous or completely obliterative pleuritis in 23 instances. There were 24 that had bronchopneumonia and 8 cases that had lobar pneumonia. Active pulmonary tuberculosis occurred in 7 cases. With regard to the liver, 6 cases had chronic passive congestion and 14 showed fatty metamorphosis.

XII. Amyloid Disease

An interesting finding which came out in this study was the high incidence of amyloid disease in our series of rheumatoid arthritis. Out of 61 cases there were 13, or 21 per cent., with amyloidosis. The organs involved were the liver, spleen, kidneys, adrenals, pancreas, and thyroid gland. The spleen was most commonly involved, being affected in 11 cases. The kidneys contained amyloid in 9 cases, the liver in 9 cases, and the adrenals in 8 cases; the pancreas and thyroid gland each in 1 case. (See Chart VI, p. 35.) It should be added that in 3 of these there was also active pulmonary tuberculosis, and this may have been a contributory ætiologic factor in the development of the amyloidosis.

It is well recognised that amyloid disease is a sequel to chronic suppuration and that it may also follow chronic, non-suppurative inflammations, yet the frequent association of amyloidosis with chronic arthritis is not mentioned in the literature A few isolated case reports are available, however. A. Imrie in 1939 described an instance of amyloidosis in a young girl having Still's disease, and H. Reiman found amyloidosis in an adult arthritic.

It is of interest to note that amyloid disease has also been found in association with acute rheumatism. Thus Beattie recorded four instances of amyloid degeneration following repeated attacks of acute rheumatism where all other causes were definitely excluded (*Brit. Med. Journ.*, 1896, 1444).

XIII. Scleromalacia Perforans

A rare condition occurred in two instances in our series. This condition is called " scleromalacia perforans." This was first described by van der Hoeve in 1934. It is a disease in which the principal

finding is the appearance of defects in the scleræ which can coalesce so that the scleræ show large gaps in which the uvea lies either covered by the conjunctiva or bare. Some men believe the process to be a degenerative one, while others say it is inflammatory. Verhoeff and King reviewed the literature in 1938 and found 14 instances of sclero-malacia perforans, 10 of which had an associated chronic rheumatoid arthritis. They noted that the microscopic findings in the scleræ markedly resembled the structure of the subcutaneous nodules found in arthritis.

One of our cases showed signs of chronic inflammatory disease having an exudate of leucocytes, and plasma cells in the sclera and episcleral tissue. This did not extend beyond the equator of the eyeball. It is possible that this condition is more common than

CHART VI.—AMYLOID DISEASE

Case No.	*Liver.*	*Spleen.*	*Kidney.*	*Adrenal.*
1	+			
2		+		
3	+	+	+	+
4	+	+	+	+
5	+	+		+
6	+	+		+
7		+	+	+
8*	+	+	+	+
9	+	+	+	+
10	+	+	+	+
11	+	+	+	
12			+	
13		+	+	
Total ..	9	11	9	8

believed, but either it is not recorded or else it is probably not recognised. Whether or not it is commonly related to chronic rheumatoid arthritis is still a matter of speculation.

XIV. CONCLUSION

1. The clinical records and available pathologic material from 61 patients having died with chronic rheumatoid arthritis have been examined.

2. Lesions indistinguishable from those found in the rheumatic heart were encountered in 19 cases (31 per cent.).

3. Six of the cases with rheumatic heart lesions had congestive heart failure as evidenced by chronic passive congestion of the liver.

* Also thyroid and pancreas.

4. Only 3 persons in the entire group had "Felty's syndrome."

5. Amyloidosis involving one or several organs was found in 13 patients (21 per cent.).

6. Glomerulitis was found in 8, 6 of which were in early subclinical stages, and the remaining 2 had clinical evidences of glomerulitis.

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REFERENCES

1. Allison, N., and Ghormley, R. E.: *Diagnosis in Joint Disease*, Wood and Company, 1931, pp. 134-194.
2. Baggenstoss, A. H., and Rosenberg, E. F.: "Cardiac Lesions in Association with Chronic Infectious Arthritis," *Arch. Int. Med.*, 1941, **67**, 241-258.
3. Bell, E. T.: "Arthritis Deformans," *Textbook of Pathology*, Lea and Febiger, 1941, pp. 903-904.
4. Bell, E. T.: "Early Stages of Glomerulitis," *Am. J. Path.*, 1936, **12**, 801-824.
5. Boas, E. P., and Rifkin, P.: "Heart in Arthritis Deformans." *J.A.M.A.*, 1924, **82**, 1596-1599.
6. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: "Valvular Diseases of the Heart with Special Reference to Pathogenesis of Old Valvular Defects," *Am. J. Path.*, 1926, **2**, 193-234.
7. Clawson, B. J., and Wetherby, M.: "Subcutaneous Nodules in Chronic Arthritis; Clinical, Pathological, and Bacteriological Studies," *Am. J. Path.*, 1932, pp. 283-294.
8. Coates, Vincent: "Kinship of Rheumatic Fever and Rheumatoid Arthritis," *M. J. & Rec.*, 1931, pp. 55-56.
9. Curtis, A. C., and Pollard, H. M.: "Felty's Syndrome: Its Several Features, including Tissue Changes, Compared with other Forms of Rheumatoid Arthritis," *Ann. Int. Med.*, 1940, **13**, 2265-2284.
10. Dawson, M. H.: "Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis," *J. Exper. Med.*, 1933, **57**, 845-858.
11. Felty, A. R.: "Chronic Arthritis in Adult Associated with Splenomegaly and Leukopenia," *Bull. Johns Hopkins Hosp.*, 1924, **35**, 16-20.
12. Froggatt, T. W.: "Incidence of Heart Lesions in Infectious Arthritis," *Lancet*, 1924, **2**, 116.
13. Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P., and Key, J. A.: "The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1937," *Ann. Int. Med.*, 1939, **12:2**, 1005; 1295.
14. Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P., and Key, J. A.: "The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1938," *Ann. Int. Med.*, 1940, **13**, 1655; 1837.
15. Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P., and Key, J. A.: "The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1939," *Ann. Int. Med.*, 1941, **14:2**, 1383; 1631.

16. VAN DER HOEVE, J.: "Scleromalacia Perforans," *Arch. Ophth.*, 1934, **11**, 111-118.
17. IMRIE, A. H., and AITKENHEAD, A. C.: "Amyloidosis Complicating Still's Disease," *Lancet*, 1939, **2**, 421-422.
18. LUX, LYDIA: "Subcutaneous Nodules Induced by Injection of *Streptococcus Viridans*," *Arch. of Path.*, 1934, **17**, 652-662.
19. MASTE, A. M., and JOFFE, H.: "Rheumatoid Arthritis and Acute Rheumatic Fever," *J.A.M.A.*, 1932, **98**, 881-882.
20. MCCRAE, THOMAS: "Arthritis Deformans: 110 Cases from Johns Hopkins Hospital," *J.A.M.A.*, 1904, **42**, 1; 94; 161.
21. MILLER, J. L.: "A Critical Review of Literature of Chronic Rheumatism," *Arch. Int. Med.*, 1936, **57**, 213-234.
22. NICHOLS, E. H., and RICHARDSON, F. S.: "Arthritis Deformans," *J. of Med. Research*, 1909, **21**, 149-221.
23. RIGLER, LEO, and WETHERBY, M.: "Roentgen Findings in Chronic Polyarticular Arthritis," *Am. J. Roent. and Radium Therapy*, 1933, **29:6**, 766-773.
24. SHAPIRO, M. J.: "Non-tuberculous Arthritis," *J.A.M.A.*, 1932, **98**, 1965-1968.
25. SINGER, H. A., and LEVY, H. A.: "Relationship of Felty's Allied Syndromes to Sepsis Lenta," *Arch. Int. Med.*, 1936, **57**, 576-600.
26. STEINBERG, C. L.: "Pathology of Atrophic Arthritis," *J. of Lab. and Clinic. Med.*, 1942, **27**, 435-442.
27. STILL, G. F.: "Chronic Joint Disease in Children," *Med.-Chir. Transactions*, London, 1896, **80**, 47.
28. VERHOEFF, F. H., and KING, MERRILL J.: "Scleromalacia Perforans," *Arch. Ophth.*, 1938, **20**, 1013.
29. WETHERBY, M.: "Incidence of Subcutaneous Nodules in Arthritis." (Personal Communication.)

BLOOD CULTURES IN RHEUMATOID ARTHRITIS

(HISTORICAL AND PERSONAL OBSERVATIONS)

BY THOMAS N. FRASER

THE problem of microbic infection in relation to the ætiology of rheumatoid arthritis has led to much discussion and experiment. Evidence of infection, particularly by streptococci, has been sought for both directly by blood cultures and indirectly by the study of immunity reactions of different kinds. The result of all this body of work remains entirely inconclusive, and it may seem redundant to burden the literature with further negative and inconclusive results.

While carrying out intensive observations on a group of cases of rheumatoid arthritis, however, a good opportunity was presented of repeating previous observations on blood cultures on this disease, and these have been contrasted in Table I. with the results of the majority of previous workers in this field.

The observations on blood cultures which have undoubtedly

attracted the greatest attention in recent years, both in Britain and America, were those of Cecil, Nicholls and Stainsby (1929), using a complicated technique in which the possibilities of contamination are clearly abundant. Recently (1940), since the present bacteriological investigations were completed, Cecil has retracted his previous results admitting the probability of contamination.

The present work was begun in 1937, before Cecil had withdrawn from his earlier position, and to constitute a direct control the same technique as that used by Cecil was carried out in its entirety. This was essentially a modification of Clawson's method (1925), and, as the table shows, this technique, or modifications of it, has been used by many other workers.

Historical

Bannatyne, Wohlman and Blaxall (1896) were the first to report the recovery of organisms in the blood of patients with rheumatoid arthritis, and were able to demonstrate the presence of a minute bacillus with marked polar staining. Others continued this work, but the percentage of positive cultures has been variable, and the organisms isolated of different types.

Cecil, Nicholls and Stainsby (1929) obtained positive blood cultures in 69 per cent. of seventy-eight patients, using their special technique referred to below. The great majority of organisms recovered were attenuated hæmolytic streptococci and were named " typical strains " by the authors. Others have repeated this work, but the majority have failed to confirm the high incidence of positive cultures obtained by Cecil. Support was received from Gray and Gowen (1931), Ashworth (1932), and Strauss (1932), and condemnation from Bernhardt and Hench (1930), Dawson, Olmstead and Boots (1932), and Wainwright (1934).

Technique of Blood Culture

The technique employed by Cecil (1929) was followed in the strictest detail, and may be summarised as follows:

Blood is withdrawn from the antecubital vein, and 10 c.c. are placed in each of two sterile centrifuge tubes, thus providing duplicate samples for the culture. After centrifuging, the supernatant serum is removed by a sterile pipette. Each tube containing blood clot is now treated in the following manner: The clot is broken up by means of a piece of hollow glass tubing, and the fragments of clot are drawn up in the same glass tube and transferred to a 3-ounce culture flask containing 50 c.c. of beef-heart infusion broth with a pH of 7·6 (0·5 per cent. sodium chloride, 1 per cent. peptone). The flask is then incubated at 37° C. and left unopened for five days.

At the end of this time subcultures are made. A tube containing

8 c.c. of a 1·5 per cent. beef-heart infusion agar is placed in a water-bath and heated until the agar is completely melted. The agar is then partially cooled; 0·5 c.c. of whole rabbit blood and 0·1 c.c. of broth from the primary culture is added to it and the contents poured into a petri dish. This subculture in a solid medium is allowed to incubate for twenty-four to forty-eight hours, and is then examined. Similar subcultures are made every three to five days until the primary culture has been in incubation for thirty days. If at the end of this time the subcultures are still sterile, the sediment in the primary culture flask is removed with a glass tube and centrifuged. Part of the sediment is examined by making stained smears, while the remainder is incubated both in fresh blood broth and on blood-agar plates. If these final subcultures show no growth, the blood culture is considered to have been sterile.

Personal Observations

1. *Rheumatoid Arthritis.*—For the investigation blood cultures were made from sixty-one patients. Fifty-one of these were women and ten were men. Their ages varied from 15 to 93 years; thirty-two were under 50 years of age and twenty-nine were 50 or over. In seventeen of the patients the disease had been present for less than a year; in twenty, from one to five years; in seven, from six to ten years; and in fourteen, for more than ten years. In three, all of whom were over 75 years of age, the duration was not obtained, but each stated that she had had the condition for many years.

All patients presented the clinical syndrome of pain, stiffness and swelling of several joints. In all but three the joints of the fingers were involved and showed the characteristic fusiform swelling associated with the disease. In two of the others the knees were affected, and in the third the elbows and shoulders. In addition to pain, stiffness, and swelling of the joints the majority showed some degree of deformity or ankylosis. As in Cecil's series, the patients were free from fever in all but two instances at the time the cultures were made. Forty-five patients were confined to bed and sixteen were ambulatory. In eleven cases the blood was taken from the patient while in the actual process of undergoing some form of physiotherapy, such as massage or passive movements, to test whether such treatment might tend to liberate organisms into the blood stream and increase the chance of obtaining positive cultures.

Streptococci were never isolated. No organisms of any kind were recovered from the blood of fifty-eight of the sixty-one patients after thirty days incubation. In the remaining three, diphtheroid bacilli were isolated. In none of the eleven patients from whom the blood was removed during physical treatment (massage or passive movements) was a positive culture obtained.

TABLE I.—SUMMARY OF RESULTS OF BLOOD CULTURES IN ARTHRITIS.

Observer.	*Year.*	*Type of Arthritis.*	*No. of Cases.*	*Positive.*		*Cases Yielding Streptococci.*			*Other Organisms.*	*Remarks.*
				Cases	%	*Hæm.* %	*Viridans.* %	*Non-hæm.* %		
Bannatyne, Wohlman and Blaxall	1896	Rheumatoid	?	3	—	—	—	—	Minute bacillus with marked polar staining	—
McCrae	1904	Arthritis deformans	?	0	0	—	—	—	—	—
Bannatyne and Lindsay	1911	Rheumatoid	2	2	—	—	—	—	Gram-positive micrococcus	—
Greene	1912	Arthritis deformans	1	1	—	—	—	—	A bacillus and a diplococcus	—
Jones	1913	Chronic	8	0	0	—	—	—	—	—
Rosenow	1914	Chronic	?	?	?	Occasional streptococcus			—	—
Crowe	1914	Acute	1	1	—	—	—	—	Micrococcus deformans	—
Rowlands	1916	Rheumatoid	?	0	0	—	—	—	—	—
Moon and Edwards	1917	Acute	40	19	48	2·5	—	32·5	Diphtheroid bacillus	Rosenow's technique.
		Chronic	83	25	30	—	—	21·6	*B. mucosus* *Staph. aureus*	—
Richards	1920	Chronic	104	14	13	—	13	—	—	—
Munro	1922	Rheumatoid	?	2	—	*Steptrococcus brevis*			—	Cultures almost uniformly negative.
Hadjopoulos and Burbank	1927	Chronic	145	29	20	6·2	4·1	—	Diphtheroid bacillus	—
									Staph. aureus	—
									Colon bacillus	
Rowlands	1927	Rheumatoid	?	0	0	—	—	—	—	—

Rowlands	1927	Rheumatoid	?	0	0	—	—	—	—	—
Surányi and Forró	1928	Polyarthritis	25	17	68	—	68	—	—	—
Cecil, Nicholls and Stainsby	1929	Chronic infectious.	78	54	69	51·3	7·6	2·5	Diphtheroid bacillus	Modification of Clawson's technique.
		Controls	54	0	0	—	—	—	*M. zymogenes*	
Rosenow	1929	Chronic	19	7	37	—	37	—	—	Modification of Cecil's technique.
Margolis and Dorsey	1930	Chronic	89	10	11	—	6·7	3·3	Diphtheroid bacillus	Various methods, including Cecil's.
Jordon and Boland	1930	Acute polyarthritis	32	12	37	—	—	—	Gram - negative bacilli Other bacilli	Modification of Cecil's technique.
Nye and Waxelbaum	1930	Acute and chronic infectious	26	5	19	—	3·9	—	Diphtheroid bacillus Gram - positive bacillus	Cecil's technique and whole blood.
Bernhardt and Hench	1930	Chronic infectious	20	5	25	—	—	—	Diphtheroids Staphylococci	Three methods, including Cecil's.
Cecil, Nicholls and Stainsby	1931	Chronic infectious	154	96	62	62	—	—	Diphtheroids	Modification of Clawson's technique.
Gray and Gowen	1931	Arthritis deformans	+110	41	37	37 "Similar to Cecil's typical strains"			—	Modification of Cecil's technique.
		Controls	74	6	8	8			—	
Kracke	1931	Chronic	—	—	30	—	—	—	Diphtheroids	—
Klugh	1931	Infectious arthritis	74	58	78	6·7 —	71·6	—	—	—
Dawson, Olmstead and Boots	1932	Chronic polyarthritis	+204	58	28	1·4 Streptococci			Gram - positive bacilli. Diphtheroids Staphylococci Gram - positive cocci Moulds	Cecil's technique. — — —

+ refers to samples of blood rather than to cases.

[*Continued overleaf*

TABLE I.—SUMMARY OF RESULTS OF BLOOD CULTURES IN ARTHRITIS—*Continued*

Observer.	*Year.*	*Type of Arthritis.*	*No. of Cases.*	*Positive.*		*Cases Yielding Streptococci.*			*Other Organisms.*	*Remarks.*
				Cases.	%	*Hæm.* %	*Viridans.* %	*Non-hæm.* %		
Wetherby and Clawson	1932	Chronic arthritis	57	32	56	1·7	42·1		Staphylococci	Clawson's technique.
		Controls	50	1	2	2				
Strauss	1932	Chronic infectious	31	17	55	6·4 Streptococci			Diphtheroids	Cecil's technique.
Ashworth	1932	Rheumatoid	138	56	40	28·2 "Similar to Cecil's typical strains"			Gram - positive diplococci Staphylococci	Modification of Cecil's technique.
Lichtman and Gross	1932	Rheumatoid	48	4	8	—	—	4·1	Gram - positive cocci	Several methods, including Cecil's.
Steinfeld	1932	Chronic	10	2	20	10	—	—	Hæmolytic diplococcus	—
Traut	1933	Chronic	38	27	71	—	—	—	Bacillary or diplococcal forms Coccoid forms	Similar to Clawson's technique.
		Controls	20	0	0	—	—	—		
Wainwright ..	1934	Rheumatoid	91	12	13	—	1	—	Diphtheroids Staphylococci Gram - positive bacilli	Similar to Cecil's technique.
McEwen, Alexander and Bunim	1936	Rheumatoid	35	7	19	3	9	5	Diphtheroids	Several methods, including Cecil's.
Angevine, Murray and Cecil	1940	Rheumatoid	+61	12	20	1 Alpha prim. strept.			Large Gram-positive diplococcus *Staph. albus* *Staph. aureus* *B. subtilis*	Aerobic clot method.
Fraser ..	1938	Rheumatoid	61	3	5	—	—	—	Diphtheroids	Cecil's technique.
		Controls	61	5	8	—	3	—	Diphtheroids	

2. *Controls.*—Blood cultures were made by Cecil's technique in sixty-one control patients. A large proportion of these were suffering from diseases due to chronic bacterial infection—*e.g.*, chronic cholecystitis, chronic osteomyelitis, etc. A complete list of the series is given in Table II.

Following Okell and Elliott (1935), blood cultures were also taken after single or multiple dental extractions from twenty patients with apical infection or pyorrhœa alveolaris who were otherwise healthy, the blood being withdrawn within ten minutes of the dental operation. These workers found that a transient bacteriæmia developed in 61 per cent. of patients after dental extractions, due to the trauma. In the majority of these the organism was a streptococcus of the viridans type. Of more importance was the fact that in 11 per cent. of patients with septic mouths a streptococcal bacteriæmia was found irrespective

TABLE II.—CONTROLS

	No. of Cases.
Dental cases	20
Chronic sinusitis	7
Chronic cholecystitis	6
Fibrositis	6
Osteo-arthritis	5
Chronic osteomyelitis	4
Peptic ulcer	4
Chronic endometritis	2
Chronic pyelitis	2
Chronic abscesses of buttocks	1
Spondylitis ankylopoietica	1
Chronic pelvic cellulitis	1
Chronic empyema	1
P.U.O.	1
Total	61

of any operative interference. It was suggested that in these patients the brushing of the teeth or the act of chewing might act as a trauma and cause a "leak" of relatively non-pathogenic organisms into the general circulation, followed by their rapid removal by the phagocytic action of the body.

Organisms were recovered from the blood of five of the sixty-one controls during thirty days incubation. In three of these the *Streptococcus viridans* was isolated and in two a diphtheroid bacillus. The former was obtained, after dental extraction for apical abscess, from the blood of three otherwise healthy patients, and the latter from patients with osteo-arthritis and fibrositis respectively.

Discussion

The results of studies on blood cultures in patients with rheumatoid arthritis have been tabulated. From this sufficiently accurate data are available for a short analysis of the findings to be given. Including my own figures, details are given of blood cultures on 1,785 samples of blood taken from 1,619 patients. Of these, 1,159 (65 per cent.) were found to be sterile, and from the remaining 626 (35 per cent.) a variety of organisms was recovered. In 418 instances (23 per cent.) the blood yielded a streptococcus, and in the remaining 208 (12 per cent.) non-streptococcal organisms were found, the most frequent of which were the diphtheroid bacillus and *Staphylococcus albus*.

From the table it will be noticed that the percentage of positive cultures obtained by various investigators varies considerably. Moreover, even among those who have obtained positive results there is a marked discrepancy in the type of organism recovered. I cannot claim that my findings in any way lessen this confusion.

Why should there be this disparity in the results obtained by various investigators ? There are some (Nye and Waxelbaum, 1930; Wainwright, 1934) who view all positive results with suspicion and consider that the organisms recovered, including the streptococci, are contaminants. The possibilities of contamination in Cecil's technique are obviously numerous, and as Dawson, Olmstead and Boots (1932) pointed out, each subculture is subjected on an average to eighteen manipulations.

On the other hand, there are those who attach significance, not only to the streptococci, but to the diphtheroid bacilli and staphylococci which they recovered from the blood. Klugh (1931), Kracke (1931), and Strauss (1932) were all of the opinion that the diphtheroid bacillus was an involution form of the streptococcus. Callow (1933), in her work on rheumatic fever, noted that 51 per cent. of the organisms isolated from the blood were pleomorphic bacilli.

Many of the positive results obtained are rendered invalid by the absence of control cultures. Lichtman and Gross (1932) stressed the necessity of providing adequate controls and included a large number in their work. In my series blood cultures were made from sixty-one controls. These included several diseases due to chronic bacterial infection, such as chronic cholecystitis and chronic osteomyelitis. In none of these was a positive blood culture obtained.

Gray (1940) sums up the position fairly by saying that the presence of bacteria in the blood stream does not prove the microbic ætiology of rheumatoid arthritis, nor does the absence of bacteria disprove it.

Summary

1. Blood cultures were made from sixty-one patients suffering from rheumatoid arthritis. The method employed was that described in 1929 by Cecil and his co-workers. Streptococci were not recovered from any of the cultures; diphtheroid bacilli were isolated from three.

2. Blood cultures from sixty-one control patients, of whom over a third were suffering from diseases due to chronic bacterial infection—*e.g.*, chronic cholecystitis, chronic osteomyelitis, etc.—*Streptococcus viridans* was recovered from the blood of three patients after dental extraction for apical abscess, and a diphtheroid bacillus from a patient with osteo-arthritis and fibrositis respectively; fifty-six cultures were sterile.

3. A brief historical survey of blood culture studies in rheumatoid arthritis has been made and tabulated. Organisms have been recovered in 35 per cent. of cases, and of these 23 per cent. yielded streptococci of various types.

4. The significance of the results of blood culture has been discussed.

5. It is not justifiable to conclude from blood culture findings that rheumatoid arthritis is a disease of infective origin.

6. It is suggested, following Okell and Elliott, that bacteriæmia, due to trauma or treatment—*e.g.*, massage—may occur and give rise to a positive blood culture; but the organisms reaching the blood may, or may quite well not, be ætiologically associated with rheumatoid arthritis.

Part of this work was undertaken while working for the Empire Rheumatism Council.

I wish to thank my colleagues at the Western Infirmary, Glasgow, for their kind co-operation.

REFERENCES

Angevine, D. M., Rothbard, S., and Cecil, R. L. (1940): Proc. Amer. Rheumatism Ass., *J. Amer. Med. Ass.*, **115**, 2111.

Ashworth, O. O . (1932): *Virg. Med. Month.*, **59**, 452.

Bannatyne, G. A., and Lindsay, J. (1911): *Brit. Med. J.*, **1**, 192.

Bannatyne, G. A., Wohlman, A. S., and Blaxall, F. R. (1896): *Lancet*, **1**, 1120.

Bernhardt, H., and Hench, P. S. (1931): *J. Infect. Dis.*, **49**, 489.

Callow, B. R. (1933): *J. Infect. Dis.*, **52**, 279.

Cecil, R. L. (1933): *J. Amer. Med. Ass.*, **100**, 1220.

Cecil, R. L. (1940): Proc. Amer. Rheumatism Ass., *J. Amer. Med. Ass.*, **115**, 2111.

Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. (1929): *Arch. Intern. Med.*, **43**, 571.

Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. (1931): *Amer. J. Med. Sci.*, **181**, 12.

Clawson, B. J. (1925): *J. Infect. Dis.*, **36**, 444.
Crowe, H. W. (1930): *J. Lab. Clin. Med.*, **15**, 1072.
Dawson, M. H., Olmstead, M., and Boots, R. H. (1932): *Arch. Intern. Med.*, **49**, 173.
Gray, J. W. (1940): Proc. Amer. Rheumatism Ass., *J. Amer. Med. Ass.*, 115, 2111.
Gray, J. W., and Gowen, C. H. (1931): *Amer. J. Med. Sci.*, **182**, 682.
Greene, H. M. (1912): *New York Med. J.*, **2**, 421.
Hadjopoulos, L. G., and Burbank, R. (1927): *J. Bone and Joint Surg.*, **25**, 278.
Jones, D. W. C. (1913): *Brit. Med. J.*, **1**, 1047.
Jordon, E. P., and Boland, J. P. (1930): *J. Infect. Dis.*, **46**, 148.
Klugh, G. F. (1931): *South. Med. J.*, **24**, 706.
Kracke, R. R. (1931): Abstract, *South. Med. J.*, **24**, 708.
Lichtman, S. S., and Gross, L. (1932): *Arch. Intern. Med.*, **49**, 1078.
McCrae, T. (1904): *J. Amer. Med. Ass.*, **42**, 1.
McEwen, C., Alexander, R. C., and Bunim, J. J. (1936): *J. Lab. Clin. Med.*, **21**, 453.
Margolis, H. M., and Dorsey, A. H. E. (1930): *J. Infect. Dis.*, **46**, 442.
Moon, V. H., and Edwards, S. R. (1917): *J. Infect. Dis.*, **21**, 154.
Munro, J. M. H. (1922): *Lancet*, **1**, 938.
Nye, R. N., and Waxelbaum, E. A. (1930): *J. Exp. Med.*, **52**, 885.
Okell, C. C., and Elliott, S. D. (1935): *Lancet*, **2**, 869.
Richards, J. H. (1920): *J. Bact.*, **5**, 511.
Rosenow, E. C. (1914): *J. Amer. Med. Ass.*, **63**, 903.
Rosenow, E. C., quoted by Margolis and Dorsey (1930): *J. Infect. Dis.*, **46**, 442.
Rowlands, M. J. (1916): *Lancet*, **1**, 133
Rowlands, M. J. (1927): *Proc. R. Soc. Med.*, **20**, 1711.
Steinfeld, F. (1932): (orig.) *Zbl. Bakt.*, **123**, 414.
Strauss, A. (1932): *Virg. Med. Month.*, **58**, 801.
Surányi, L., and Forró, E. (1928): *Klin. Wschr.*, **7**, 453.
Traut, E. F. (1933): *J. Infect. Dis.*, **52** 230.
Wainwright, C. W. (1934): *J. Amer. Med. Ass.*, **103**, 1357.
Wetherby, M., and Clawson, B. J. (1932): *Arch. Intern. Med.*, **49**, 303.

CORRESPONDENCE

Sir,—The following are a few points which occur to me on reading Dr. Hughes' paper on Resistance in Rheumatism.

The basis of the whole paper seems to be invalidated by a confusion between hypersensitivity and resistance, as is shown by the example quoted of Koch's phenomenon and the tuberculin test, both of which are the result of hypersensitivity or allergy, and not necessarily connected with the degree of resistance. It is now established that hypersensitivity can occur independently of high resistance and *vice versa*, though admittedly they are often coincidences. Therefore, if the analogy between the effect of measles, pregnancy, etc., on the tuberculin

reaction and on rheumatism holds good, it is the hypersensitivity that is reduced and there is no evidence at all to show that the resistance is either raised or lowered. A similar argument applies in connection with the Leprolin reaction in leprosy. The characteristic destructive lesion of adult tuberculosis and the lesions of rheumatism and leprosy are generally regarded as being due not to the direct effect of the reaction between the resisting host and the invading organism but as the product of hypersensitivity on the part of the host. The effect of high resistance in the absence of allergy is shown by the healed calcified primary complex in the case of tuberculosis.

The conception of the lesion of tuberculosis or rheumatism as "designed" for the purpose of resisting infection is highly unscientific to say the least. In fact, the evidence provided by Rich's work is all the other way. Furthermore, "resistance" does not depend entirely or even mainly on a local cellular reaction, but also on a general humoral mechanism.

Hill and Martin's work on the suppression of anaphylaxis by various agents does not seem to have anything whatever to do with the problem at issue. Anaphylaxis is not now regarded as playing any part in the defence mechanism of the body, and is generally held to be an undesirable side-effect due to hypersensitivity.

The effect of malaria on G.P.I. is beside the point. It is generally held to be due to the effect of the high temperature on the organism, and the immunological reactions of the host are not directly involved.

What the author's thesis seems to amount to is this: measures designed to decrease hypersensitivity—that is to say, desensitisation—are successful in the treatment of rheumatism, and in this he is doubtless quite correct; but on the other hand he is guilty of a certain amount of loose thinking about the term resistance, as used in connection with rheumatism. The exact meaning of the term is vague, and no one has yet been able to demonstrate exactly what the resistance of the body is supposed to be directed against, and until a direct connection has been shown to exist between the lesion of rheumatism and a specific infecting organism the use of the term resistance is perhaps unsatisfactory.

I am, etc.,

I. R. S. GORDON.

BATH.
February 25, 1943.

EDITORIAL

The Heberden Society awarded its medal in 1940 for original work and research in Rheumatology to Lieutenant-Colonel Copeman, F.R.C.P., R.A.M.C., for his communication on "Improvised Methods of Physical Treatment of Rheumatism in the Field." It has selected for its next award another member of the Editorial Committee of the Annals, Dr. Philip Hench, of the Mayo Clinic, for his work on "The Effect of Jaundice in Rheumatoid Arthritis." Dr. Hench, who is now Lieutenant-Colonel in the United States Medical Corps, hopes to continue these studies after the War and may be able to study fresh aspects of the subject under the conditions of military service.

In acknowledging the award Dr. Hench writes to the Heberden Society: "I know that this award is not merely an expression of your interest in my own work. It is more particularly and more importantly a gracious symbol of your sympathetic approval of the work of the American Rheumatism Association, the organisation in this country which is trying to accomplish aims essentially similar to those which the Heberden Society and the Empire Rheumatism Council are so ably accomplishing in your country despite the difficulties of war. American physicians are proud to join with you in your humanitarian efforts on behalf of the rheumatism sufferers everywhere, but to continue the efforts we must have a world in which the word humanitarianism has some meaning, and to guarantee such a world the people of our countries are again firmly joined. Here's to the day when American and British rheumatologists may again meet with other men of science in an atmosphere of lasting peace and hope."

The Heberden Society, which takes its title from a distinguished physician who was one of the early British students of rheumatic diseases and whose name is associated with a form of chronic arthritis, was founded in 1936 for the advancement of the study of rheumatic diseases. The Society's bronze medal, designed and struck by the Goldsmiths and Silversmiths' Company, was inaugurated in 1938, and is awarded from time to time for original work of distinction in this field.

We have received the following Medical Journals: *Revista Argentina de Rheumatologia*, *El Dia Medico*, Buenos Aires, *Revista Medica de Chile*, *Revista de Sanidad y Assistencia Social*. We hope to review articles on rheumatic diseases appearing in them when circumstances permit, and in the meantime note with satisfaction the interest which is being taken in the problems presented by rheumatism in South America.

[*To face last page of text.*

MILK INTOLERANCE

Milk in various forms, both modified and unmodified, and the curd formations consequent upon contact with the gastric juices.

RAW MILK

PASTEURISED MILK

BOILED MILK—*The milk was momentarily brought to boiling point.*

DILUTED MILK—*1 part milk and 1 part water.*

LACTIC ACID MILK (Special)—*Lactic Acid B.P. added drop by drop until milk just begins to curdle*

LACTIC ACID MILK—*30 drops of lactic acid B.P. added per pint of milk.*

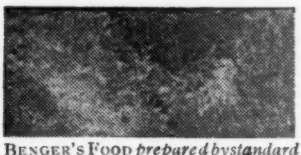
CITRATED MILK—*1.5 grains of sodium citrate added to 1 fl. oz. of raw milk.*

CITRATED MILK (Boiled)—*1.5 grains of sodium citrate added to 1 fl. oz. of raw milk and the mixture brought to the boil*

DILUTED MILK—*1 part milk and 2 parts water.*

MILK AND BARLEY WATER—*1 part milk to 1 part Barley Water.*

MILK AND CREAM—*1 part milk to 1 part cream.*



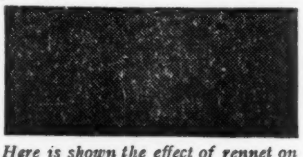
BENGER'S FOOD *prepared by standard formula and self-digested for 5 mins.*

BENGER'S FOOD *prepared by standard formula and self-digested for 15 mins.*

BENGER'S FOOD *prepared by standard formula and self-digested for 30 mins.*

An infant's gastric juice contains the enzyme rennin rather than pepsin.

This photograph shows the effect of rennet on Human Milk adjusted to pH 4.6.



Here is shown the effect of rennet on Benger's Food prepared by Formula 1 and adjusted to pH 4.6.

★ *A short monograph on this subject has been published by Benger's Ltd., Holmes Chapel, Cheshire, and is available to any member of the medical profession forwarding his or her card.*

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